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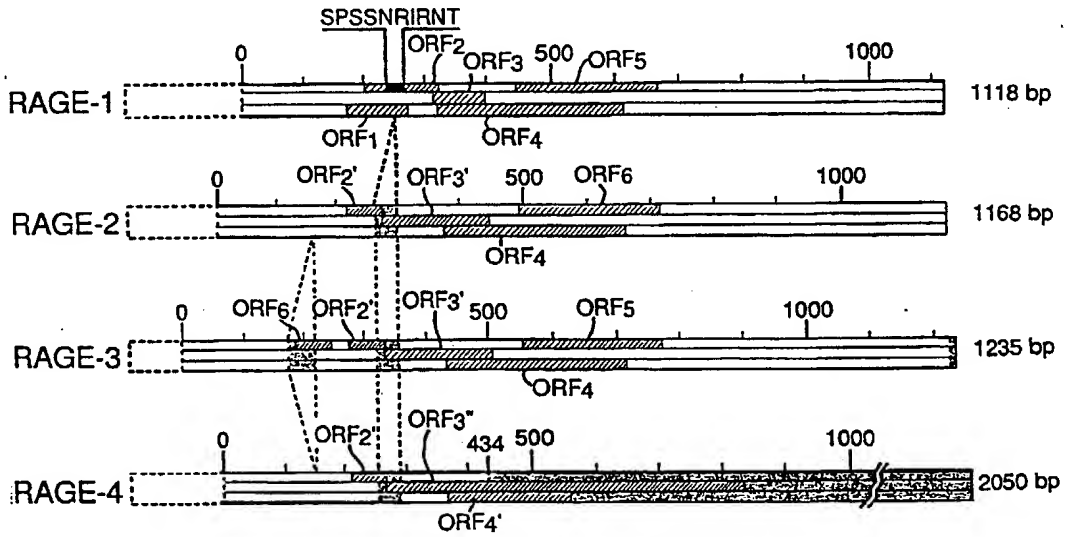
(54) Title: RAGE TUMOR REJECTION ANTIGENS



(57) Abstract

The invention describes the RAGE tumor rejection antigen precursor family, including nucleic acids encoding such tumor rejection antigen precursors, tumor rejection antigen peptides or precursors thereof and antibodies relating thereto. Methods and products also are provided for diagnosing and treating conditions characterized by expression of a RAGE tumor rejection antigen precursor.

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RAGE TUMOR REJECTION ANTIGENS

Field of the Invention

This invention relates to nucleic acid molecules which code for tumor rejection antigens and precursors thereof. The tumor rejection antigen precursors are processed, *inter alia*, into at least one tumor rejection antigen that is presented by HLA molecules. The nucleic acid molecules, proteins coded for by such molecules and peptides derived therefrom, as well as related antibodies and cytotoxic lymphocytes, are useful, *inter alia*, in diagnostic and therapeutic contexts.

Background of the Invention

The process by which the mammalian immune system recognizes and reacts to foreign or alien materials is complex. An important facet of the system is the T cell response. T cells can recognize and interact with other cells via cell surface complexes on the other cells of peptides and molecules referred to as human leukocyte antigens ("HLA") or major histocompatibility complexes ("MHCs"). The peptides are derived from larger molecules which are processed by the cells which also present the HLA/MHC molecule. See Male et al., Advanced Immunology (J.P. Lipincott Company, 1987), especially chapters 6-10. The interaction of T cells and complexes of HLA/peptide is restricted, requiring a specific T cell for a specific complex of an HLA molecule and a peptide. If a specific T cell is not present, there is no T cell response even if its partner complex is present. Similarly, there is no response if the specific complex is absent, but the T cell is present. The mechanism is involved in the immune system's response to foreign materials, in autoimmune pathologies, and in responses to cellular abnormalities.

The mechanism by which T cells recognize alien materials also has been implicated in cancer. A number of cytolytic T lymphocyte (CTL) clones directed against autologous melanoma have been described. In some instances, the antigens recognized by these clones have been characterized. In PCT application PCT/US92/04354, published on November 26, 1992, the "MAGE" family, a tumor specific family of genes, is disclosed. The expression products of these genes are processed into peptides which, in turn, are expressed on cell surfaces. This can lead to lysis of the tumor cells by specific CTLs. The genes are said to code for "tumor rejection antigen precursors" or "TRAP" molecules, and the peptides derived therefrom are referred to as "tumor rejection antigens" or "TRAs". See Traversari et al., Immunogenetics 35: 145 (1992); van der Bruggen et al., Science 254: 1643 (1991), for further information on this family of genes. Also, see U.S. Patent No. 5,342,774.

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In U.S. Patent 5,405,940, MAGE nonapeptides are taught which are presented by the HLA-A1 molecule. Given the known specificity of particular peptides for particular HLA molecules, one should expect a particular peptide to bind one HLA molecule, but not others. This is important, because different individuals possess different HLA phenotypes. As a result, while identification of a particular peptide as being a partner for a specific HLA molecule has diagnostic and therapeutic ramifications, these are only relevant for individuals with that particular HLA phenotype. There is a need for further work in the area, because cellular abnormalities are not restricted to one particular HLA phenotype, and targeted therapy requires some knowledge of the phenotype of the abnormal cells at issue.

It also was discovered that a MAGE expression product is processed to a second TRA. This second TRA is presented by HLA-C clone 10 molecules. Therefore, a given TRAP can yield a plurality of TRAs.

In PCT WO94/14459, published July 7, 1994, tyrosinase is described as a tumor rejection antigen precursor. This reference discloses that a molecule which is produced by some normal cells (e.g., melanocytes), is processed in tumor cells to yield a tumor rejection antigen that is presented by HLA-A2 molecules.

In PCT WO94/21126, published September 29, 1994, a second TRA, not derived from tyrosinase is taught to be presented by HLA-A2 molecules. The TRA is derived from a TRAP, but is coded for by a non-MAGE gene. This disclosure shows that a particular HLA molecule may present TRAs derived from different sources.

In PCT WO95/00159, published January 5, 1995, an unrelated tumor rejection antigen precursor, the so-called "BAGE" precursor, is described. TRAs are derived from the TRAP and also are described. They form complexes with MHC molecule HLA-C-Clone 10.

In PCT WO95/03422, published February 2, 1995, another unrelated tumor rejection antigen precursor, the so-called "GAGE" precursor, is described. The GAGE precursor is not related to the BAGE or the MAGE family.

The work which is presented by the papers, patents and patent applications described above deal, for the most part, with the MAGE family of genes, the BAGE gene and the GAGE gene. These genes are expressed in a number of tumors but are completely silent in normal tissues except testis. None is expressed in renal carcinoma.

It now has been discovered that another gene family, the "RAGE" genes, encodes additional tumor rejection antigens and precursors thereof. The RAGE genes do not show homology to the MAGE family of genes, to the BAGE gene or the GAGE gene. The RAGE genes are expressed in renal tumor cells, but not in normal renal cells. The RAGE genes are also expressed in certain other tumor cell types.

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The invention is elaborated upon in the disclosure which follows.

Summary of the Invention

The invention provides isolated nucleic acid molecules, expression vectors containing those molecules and host cells transfected with those molecules. The invention also provides isolated proteins and peptides, and antibodies to those proteins and peptides. Kits containing the foregoing molecules additionally are provided. The foregoing can be used in the diagnosis or treatment of conditions characterized by the expression of a RAGE TRA or TRAP.

According to one aspect of the invention, an isolated polypeptide is provided. It includes at least the amino acid sequence of SEQ.ID.NO.40 and is a RAGE TRA. In preferred embodiments, the isolated polypeptide includes at least the amino acid sequence of SEQ.ID.NO. 43. In other embodiments the isolated polypeptide may consist essentially of or may even be only the amino acid sequence of SEQ.ID.NO.40 or SEQ.ID.NO.43.

According to another aspect of the invention, an isolated nucleic acid molecule is provided. The molecule encodes a polypeptide selected from the group consisting of SEQ.ID.NO.40 and SEQ.ID.NO.43. The isolated nucleic acid can include SEQ.ID.NO.44 and preferably includes SEQ.ID.NO.45. In other embodiments the isolated nucleic acid may consist essentially of or may even be only SEQ.ID.NOs.44 or 45.

According to another aspect of the invention, an isolated nucleic acid molecule is provided which hybridizes under stringent conditions to a molecule consisting of the nucleic acid sequence of SEQ.ID.NO.1, SEQ.ID.NO.4, SEQ.ID.NO.6, SEQ.ID.NO.10, SEQ.ID.NO.12, SEQ.ID. NO.13, SEQ.ID.NO.14, SEQ.ID.NO.15, SEQ.ID.NO.17, SEQ.ID.NO.23, and/or SEQ.ID.NO.35, and which codes for RAGE TRAs or TRAPs, with the proviso that the isolated nucleic acid molecule does not code for a MAGE, GAGE or BAGE TRA or TRAP. In preferred embodiments, the isolated nucleic acid molecule is an mRNA molecule or a cDNA molecule. In one embodiment, the isolated nucleic acid molecule is complementary to nucleotides selected from the group consisting of 204 to 326 of SEQ.ID.NO.1, 313 to 399 of SEQ.ID.NO.1, 444 to 665 of SEQ.ID.NO.1, 273 to 449 of SEQ.ID.NO.12, 217 to 276 of SEQ.ID.NO.12, 185 to 247 of SEQ.ID.NO.13 and 269 to 832 of SEQ.ID.NO.14. In another embodiment, the isolated nucleic acid consists essentially of SEQ.ID.NO.1, SEQ.ID.NO.4, SEQ.ID. NO.6, SEQ.ID.NO.10, SEQ.ID.NO.12, SEQ.ID. NO.13, SEQ.ID.NO.14, SEQ.ID.NO.15, SEQ.ID.NO.17, SEQ.ID.NO.23, SEQ.ID.NO.35, SEQ.ID.NO.44 and/or SEQ.ID.NO.45.

According to another aspect of the invention, expression vectors and host cells containing those expression vectors are provided. The expression vectors include any one or more of the isolated nucleic acid

molecules described above. In one embodiment, the expression vector comprises the isolated nucleic acid of SEQ.ID.NOs.44 or 45. Other expression vectors according to the invention include the isolated nucleic acids described above and a nucleic acid which codes for an HLA molecule which can present the TRAs of the invention to cytolytic T cells. One example is HLA-B7. The host cells may endogenously express the HLA molecule such as HLA-B7.

According to another aspect of the invention, isolated nucleic acid molecules that are unique fragments of SEQ.ID.NO.1, SEQ.ID.NO.12, SEQ.ID.NO.13 or SEQ.ID.NO.14 or their complements are provided. Such unique fragments are used to identify or to selectively amplify the nucleic acids described above. When the unique fragments are used for identifying expression of the above nucleic acids, the unique fragments preferably are between 200 and 1310 nucleotides in length, 200 and 1234 nucleotides in length, 200 and 2050 nucleotides in length or 200 and 1167 nucleotides in length. When the unique fragments are used to amplify the above-described nucleic acid molecules, the unique fragments are between 12 and 32 nucleotides in length. It will be recognized that amplification procedures are not exclusive of procedures that might be used to identify a nucleic acid molecule.

According to another aspect of the invention, kits for detecting the presence of expression of a TRA or TRAP are provided. Such kits employ two or more of the above-described molecules isolated in separate containers and packaged in a single package. In one such kit, a pair of amplification primers are provided, each of the pair consisting essentially of a 12-32 in length nucleotide contiguous segment of SEQ.ID.NO.1 or the complement thereof, SEQ.ID.NO.12 or the complement thereof, SEQ.ID.NO.13 or the complement thereof, or SEQ.ID.NO.14 or the complement thereof, and wherein the contiguous segments are non-overlapping. Preferably the amplification primers are PCR primers, wherein one of the primers is a contiguous segment of the Watson strand and another of the primers is the complement of a contiguous segment of Crick strand. In certain embodiments, primers are constructed and arranged to selectively amplify and/or identify only one of the RAGE family, such as only RAGE 1 or a portion of only RAGE 1, etc. For example, one of the pair can be contiguous in RAGE 1 genes and allelic variants thereof but not contiguous in RAGE 2, 3 or 4 genes. More specifically as an example , a first primer can be a nucleic acid consisting essentially of any one of SEQ.ID.NOs.50-57, and a second primer can consist essentially of a 12-32 in length nucleotide contiguous segment of SEQ.ID.NO.1, or the complement thereof, depending upon the choice of the first primer.

Another kit according to the invention is an expression kit comprising a separate portion of the isolated nucleic acid molecule which codes for a RAGE TRAP, or a molecule including a RAGE TRA, and an HLA presenting molecule that forms a complex with that TRA and that stimulates a cytolytic T cell

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response. One such kit includes a nucleic acid which codes for the peptide of SEQ.ID.NO.40 or SEQ.ID.NO.43 and a nucleic acid molecule which codes for HLA-B7. Another kit according to the invention is an expression kit comprising a separate portion of the isolated nucleic acid molecule which hybridizes under stringent conditions to a molecule consisting of the nucleic acid sequence of SEQ.ID.NO.1. SEQ.ID.NO.4. SEQ.ID.NO.6, SEQ.ID.NO.10. SEQ.ID.12. SEQ.ID.13. SEQ.ID.14. SEQ.ID.15. SEQ.ID.17. SEQ.ID.23 and/or SEQ.ID.35 and which codes for a RAGE TRAP. and a nucleic acid molecule which codes for HLA-B7.

According to another aspect of the invention isolated TRAPs coded for by the above molecules and useful fragments thereof also are provided. Antibodies to such molecules and to complexes of HLA and RAGE TRAs also are provided.

According to another aspect of the invention. methods for diagnosing a disorder characterized by expression of a RAGE TRAP are provided. One method involves a RAGE TRAP which is processed to a RAGE derived TRA that forms a complex with HLA molecules. The method involves contacting a biological sample isolated from a subject with an agent that binds the complex and then determining binding between the complex and the agent as a determination of the disorder. In one embodiment. the method determines binding of the agent to a complex of RAGE TRA and HLA-B7. In this embodiment. the RAGE TRA can be selected from the group consisting of the peptide of SEQ.ID.NO.40 and the peptide of SEQ.ID.NO.43. Another method involves contacting a biological sample isolated from a subject with an agent that is specific for a RAGE nucleic acid or an expression product thereof. Interaction between the agent and the nucleic acid or expression product thereof then is determined. interaction being indicative of the disorder. The agent may be a nucleic acid which hybridizes under stringent conditions to a molecule consisting of the nucleic acid sequence selected from the group consisting of SEQ.ID.NO.1. SEQ.ID.NO.4. SEQ.ID.NO.6. SEQ.ID.NO.10. SEQ.ID.NO.12. SEQ.ID. NO.13. SEQ.ID.NO.14. SEQ.ID.NO.15. SEQ.ID.NO.17. SEQ.ID.NO.23 and SEQ.ID.NO.35. and which codes for a TRAP. with the proviso that the isolated nucleic acid molecule does not code for a MAGE. GAGE. or BAGE TRAP. Another method involves contacting a biological sample isolated from a subject with an agent that is specific for a RAGE tumor rejection antigen peptide and then determining interaction between the peptide and the agent as a determination of the disorder. In one embodiment. the peptide is selected from the group consisting of SEQ.ID.NO.40 and SEQ.ID.NO.43.

According to another aspect of the invention. an isolated biological preparation is provided. The preparation consists essentially of cytolytic T cells specific for complexes of an HLA molecule and a RAGE TRA. In one embodiment. the cytolytic T cells are specific for complexes of an HLA-B7 molecule and the

TRA. In this embodiment, the antigen can be a peptide selected from the group consisting of the peptide of SEQ.ID.NO.40 and the peptide of SEQ.ID.NO.43.

Another aspect of the invention thus involves a method for enriching selectively a population of T cells with cytolytic T cells specific for complexes of an HLA molecule and a RAGE TRA. The method involves contacting an isolated population of T cells containing cytolytic T cell precursors with an agent resulting in presentation of a complex of a RAGE TRA and HLA presenting molecule, in an amount sufficient to selectively enrich the isolated population of T cells with said cytolytic T cells. In one preferred embodiment, the HLA molecule is HLA-B7 and the RAGE TRA is selected from the group consisting of a peptide consisting of the amino acids of SEQ.ID.NO.40 and a peptide consisting of the amino acids of SEQ.ID.NO.43.

Still another aspect of the invention involves methods for treating a subject with a disorder characterized by expression of a RAGE TRA or TRAP. One such method involves administering to a subject in need of such treatment an effective amount of an agent which enriches selectively in the subject the presence of complexes of HLA and RAGE TRA, resulting in cytolytic T cell response reactive with such complexes, sufficient to ameliorate the disorder. Such agents include the RAGE TRAPs and recombinant cells expressing complexes of the HLA and RAGE TRA. In one embodiment, such agents include cells expressing a complex of HLA-B7 and a peptide consisting of the peptide of SEQ.ID.NO.40 or the peptide of SEQ.ID.NO.43. Another method involves administering to a subject in need of such treatment an amount of autologous cytolytic T cells sufficient to ameliorate the disorder, wherein the autologous cytolytic T cells are specific for complexes of an HLA molecule and a RAGE TRA.

In connection with any isolated nucleic acid encoding a TRAP or TRA as described above, the invention also embraces degenerate nucleic acids that differ from the isolated nucleic acid in codon sequence only due to the degeneracy of the genetic code or complements of any of the foregoing nucleic acids.

The invention also embraces functional variants and equivalents of all of the molecules described above.

The invention also involves the discovery and isolation of TRAPs and TRAs which are expressed in tumor cells, particularly in renal tumor cells, and not expressed in normal renal cells. Prior to the present invention, TRAPs and/or TRAs of the type described herein were not known and identified for renal carcinomas, despite the knowledge and identity of other TRAPs and TRAs for numerous other cell types. Surprisingly, the RAGE-1 gene of the present invention was expressed in only 1 of 57 renal carcinomas, and the best antigenic peptide for a particular cytotoxic T cell clone was discovered to be a decamer, not the usual nonamer peptide. Thus, according to another aspect of the invention, the invention provides TRAPs, TRAs

and nucleic acids coding for TRAPs and TRAs, which are not MAGE, BAGE AND GAGE TRAPs. TRAs and nucleic acids, which are expressed in tumor cells, particularly in renal tumor cells but not in normal renal cells, and are obtainable by a process comprising

isolating renal tumor cells from a patient,

isolating lymphocytes from the patient,

contacting the renal tumor cells with the lymphocytes in vitro,

isolating a cytotoxic T cell clone among the lymphocytes reactive with the renal tumor cells,

preparing an expression library from mRNA of the renal tumor cells,

screening the expression library with the cytotoxic T cell clone for a library member reactive with the cytotoxic T cell clone,

isolating said library member reactive with the cytotoxic T cell clone, and

sequencing the renal cell nucleic acid in said library member, said renal cell nucleic acid encoding the TRAP (or portion thereof) including the TRA. The invention also provides sequences having homology to such nucleic acids and coding for renal associated TRAPs and TRAs, sequences which hybridize under stringent conditions to such nucleic acids and coding for renal associated TRAPs and TRAs, complements, unique fragments and 'degenerates' of the foregoing, the TRAPs and TRAs themselves, as well as functional variants and equivalents of any of the foregoing, all of which can be considered to be RAGE nucleic acids, TRAPs and TRAs.

The invention also provides agents that selectively enrich in a subject the presence of complexes of HLA/RAGE TRAs for use as a medicament. Such agents include, but are not limited to, RAGE TRAs and/or RAGE TRAPs; recombinant cells expressing RAGE TRAs and/or RAGE TRAPs and also expressing appropriate HLA molecules, recombinant or not; and functional variants and equivalents of the foregoing. Specific examples include the RAGE TRA of SEQ.ID.NO. 43: any fragment of the RAGE TRAP of SEQ.ID.NO. 5 including the TRA of SEQ.ID.NO. 43: the RAGE TRAP of SEQ.ID.NO. 5: recombinant cells expressing the TRA of SEQ.ID.NO. 43 and HLA-B7; and/or any other RAGE TRA, RAGE TRAP or functional fragment thereof and/or cells expressing such molecules.

The invention also provides agents that selectively enrich in a subject the presence of complexes of HLA/RAGE TRAs in the manufacture of a medicament for treating cancer. Such agents include, but are not limited to, RAGE TRAs and/or RAGE TRAPs; recombinant cells expressing RAGE TRAs and/or RAGE TRAPs and also expressing appropriate HLA molecules, recombinant or not; and functional variants and equivalents of the foregoing. Specific examples include the RAGE TRA of SEQ.ID.NO. 43: any fragment of the RAGE TRAP of SEQ.ID.NO. 5 including the TRA of SEQ.ID.NO. 43: the RAGE TRAP of

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SEQ.ID.NO. 5; recombinant cells expressing the TRA of SEQ.ID.NO. 43 and HLA-B7; and/or any other RAGE TRA, RAGE TRAP or functional fragment thereof and/or cells expressing such molecules.

The invention also provides cytotoxic T cells specific for complexes of HLA and RAGE TRA for use as a medicament. One nonlimiting example is autologous cytotoxic T cells specific for tumor cells expressing complexes of HLA-B7 and RAGE TRA.

The invention also provides cytotoxic T cells specific for complexes of HLA and RAGE TRA in the manufacture of a medicament for treating cancer. One nonlimiting example is autologous cytotoxic T cells specific for tumor cells expressing complexes of HLA-B7 and RAGE TRA.

The invention also provides pharmaceutical preparations containing any one or more of the medicaments described above or throughout the specification. Such pharmaceutical preparations can include pharmaceutically acceptable diluent carriers or excipients.

These and other objects of the invention will be described in further detail in connection with the detailed description of the invention.

Brief Description of the Drawings

Figure 1 is a graph showing the levels of tumor necrosis factor produced when CTL Clone 263/17 is combined with COS cells transfected with HLA-B7 cDNA and a cDNA encoding a RAGE TRAP.

Figure 2 is a schematic representation of the RAGE-1, 2, 3 and 4 cDNAs. Closed black boxes indicate the different ORF in each of the three reading frames. Shaded areas in the RAGE-2, 3 and 4 cDNAs represent sequences that are unrelated to the RAGE-1 sequence, including two insertions. The 5' terminal sequence obtained by PCR is indicated with dashed boxes. The 3' end of this PCR sequence is identical to the overlapping 5' end sequences of the RAGE-2, 3 and 4 cDNAs. The antigenic peptide encoded by RAGE-1 is indicated.

Figure 3 is a graph showing the levels of tumor necrosis factor produced when CTL Clone 263/17 is combined with COS cells transfected with HLA-B7 cDNA and a cDNA encoding a RAGE TRAP or a minigene encoding ORF2 of a RAGE TRAP.

Figure 4 is a graph detailing the levels of tumor necrosis factor produced when CTL Clone 263/17 is combined with peptide fragments of the TRAP encoded by ORF2 of the RAGE gene and COS cells transfected with HLA-B7.

Figure 5 is a graph depicting the lytic activity of CTL clone 267/17 against HLA-B7$^-$ LB23-EBV B cells pulsed with increasing concentrations of the peptides including a RAGE TRA.

Brief Description of the Sequences

SEQ.ID.NO.1 is the nucleotide sequence of the RAGE-1 cDNA.

SEQ.ID.NO.2 is open reading frame 1 (ORF1) of the cDNA of SEQ.ID.NO.1.

SEQ.ID.NO.3 is the translated amino acid sequence of SEQ.ID.NO.2.

SEQ.ID.NO.4 is open reading frame 2 (ORF2) of the cDNA of SEQ.ID.NO.1.

SEQ.ID.NO.5 is the translated amino acid sequence of SEQ.ID.NO.4.

SEQ.ID.NO.6 is open reading frame 3 (ORF3) of the cDNA of SEQ.ID.NO.1.

SEQ.ID.NO.7 is the translated amino acid sequence of SEQ.ID.NO.6.

SEQ.ID.NO.8 is open reading frame 4 (ORF4) of the cDNA of SEQ.ID.NO.1.

SEQ.ID.NO.9 is the translated amino acid sequence of SEQ.ID.NO.8.

SEQ.ID.NO.10 is open reading frame 5 (ORF5) of the cDNA of SEQ.ID.NO.1.

SEQ.ID.NO.11 is the translated amino acid sequence of SEQ.ID.NO.10.

SEQ.ID.NO.12 is the nucleotide sequence of the RAGE-2 cDNA.

SEQ.ID.NO.13 is the nucleotide sequence of the RAGE-3 cDNA.

SEQ.ID.NO.14 is the nucleotide sequence of the RAGE-4 cDNA.

SEQ.ID.NO.15 is open reading frame 2' (ORF2') of the cDNA of SEQ.ID.NO.12.

SEQ.ID.NO.16 is the translated amino acid sequence of SEQ.ID.NO.15.

SEQ.ID.NO.17 is open reading frame 3' (ORF3') of the cDNA of SEQ.ID.NO.12.

SEQ.ID.NO.18 is the translated amino acid sequence of SEQ.ID.NO.17.

SEQ.ID.NO.19 is open reading frame 4 (ORF4) of the cDNA of SEQ.ID.NO.12.

SEQ.ID.NO.20 is the translated amino acid sequence of SEQ.ID.NO.19.

SEQ.ID.NO.21 is open reading frame 5 (ORF5) of the cDNA of SEQ.ID.NO.12.

SEQ.ID.NO.22 is the translated amino acid sequence of SEQ.ID.NO.21.

SEQ.ID.NO.23 is open reading frame 6 (ORF6) of the cDNA of SEQ.ID.NO.13.

SEQ.ID.NO.24 is the translated amino acid sequence of SEQ.ID.NO.23.

SEQ.ID.NO.25 is open reading frame 2' (ORF2') of the cDNA of SEQ.ID.NO.13.

SEQ.ID.NO.26 is the translated amino acid sequence of SEQ.ID.NO.25.

SEQ.ID.NO.27 is open reading frame 3' (ORF3') of the cDNA of SEQ.ID.NO.13.

SEQ.ID.NO.28 is the translated amino acid sequence of SEQ.ID.NO.27.

SEQ.ID.NO.29 is open reading frame 4 (ORF4) of the cDNA of SEQ.ID.NO.13.

SEQ.ID.NO.30 is the translated amino acid sequence of SEQ.ID.NO.29.

SEQ.ID.NO.31 is open reading frame 5 (ORF5) of the cDNA of SEQ.ID.NO.13.

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SEQ.ID.NO.32 is the translated amino acid sequence of SEQ.ID.NO.31.

SEQ.ID.NO.33 is open reading frame 2' (ORF2') of the cDNA of SEQ.ID.NO.14.

SEQ.ID.NO.34 is the translated amino acid sequence of SEQ.ID.NO.33.

SEQ.ID.NO.35 is open reading frame 3''(ORF3'') of the cDNA of SEQ.ID.NO.14.

SEQ.ID.NO.36 is the translated amino acid sequence of SEQ.ID.NO.35.

SEQ.ID.NO.37 is open reading frame 4' (ORF4') of the cDNA of SEQ.ID.NO.14.

SEQ.ID.NO.38 is the translated amino acid sequence of SEQ.ID.NO.37.

SEQ.ID.NO.39 is the dodecamer peptide containing the RAGE tumor rejection antigen mentioned in connection with Figure 4.

SEQ.ID.NO.40 is a nonamer fragment (amino acids 1-9) of the peptide described in SEQ.ID.NO.39.

SEQ.ID.NO.41 is a nonamer fragment (amino acids 2-10) of the peptide described in SEQ.ID.NO.39.

SEQ.ID.NO.42 is a nonamer fragment (amino acids 3-11) of the peptide described in SEQ.ID.NO.39.

SEQ.ID.NO.43 is a decamer fragment (amino acids 1-10) of the peptide described in SEQ.ID.NO.39.

SEQ.ID.NO.44 is the nucleotide sequence of a DNA which encodes the peptide of SEQ.ID.NO.40.

SEQ.ID.NO.45 is the nucleotide sequence of a DNA which encodes the peptide of SEQ.ID.NO.43.

SEQ.ID.NO.46 is a sense primer used in PCR tests for expression of the RAGE TRAP.

SEQ.ID.NO.47 is an antisense primer used in PCR tests for expression of the RAGE TRAP, common to all RAGE genes tested.

SEQ.ID.NO.48 is an antisense primer, specific for RAGE-1, used in PCR tests for expression of the RAGE-1 TRAP gene.

SEQ.ID.NO.49 represents the region of RAGE genes flanking the insertion point of ORF2, with the insertion designated by N.

SEQ.ID.NOs.50-57 are PCR primers useful in identification of RAGE 1.

Detailed Description of the Invention

An antigen recognized on a renal cell carcinoma by autologous CTL restricted by HLA-B7 is encoded by a previously unknown gene. This gene is silent in all normal tissues (including testis), except for retina, and it is expressed in several tumor samples.

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EXAMPLE 1: Description of an anti-renal cell carcinoma CTL clone of patient LE9211

Tumor line LE9211-RCC is a renal cell carcinoma line derived from a tumor sample of a female patient named LE9211. A sample thereof was irradiated, so as to render it non-proliferative. These irradiated cells were then used to isolate cytolytic T cell clones ("CTLs") specific thereto.

A sample of peripheral blood mononuclear cells ("PBMCs") was taken from patient LE 9211, and contacted to the irradiated carcinoma cells. After 14 days, the mixture was observed for lysis of the carcinoma cells, which indicated that CTLs specific for a complex of peptide and HLA molecule presented by the carcinoma cells were present in the sample.

The lysis assay employed was a chromium release assay following Herin et al., Int. J. Cancer 39:390-396 (1987). The assay, however, is briefly described herein. The target carcinoma cells were grown *in vitro*, and then resuspended at 10^7 cells/ml in Dulbecco's Modified Eagles Medium (DMEM), supplemented with 30% FCS, and incubated for 45 minutes at 37°C with 200 µCi/ml of $Na(^{51}Cr)O_4$. Labeled cells were washed three times with DMEM. These were then resuspended in DMEM supplemented with 10 mM Hepes and 10% fetal calf serum (FCS), after which 100 µl aliquots containing 10^3 cells were distributed into 96 well microplates. Samples of lymphocytes were added in 100 µl of the same medium, and assays were carried out in duplicate. Plates were centrifuged for 4 minutes at 100g and incubated for four hours at 37°C in a 8% CO_2 atmosphere.

Plates were centrifuged again, and 100 µl aliquots of supernatant were collected and counted. Percentage of ^{51}Cr release was calculated as follows:

$$\%\ ^{51}Cr\ release = \frac{(ER-SR)}{(MR-SR)} \times 100$$

where ER is observed, experimental ^{51}Cr release, SR is spontaneous release measured by incubating 10^3 labeled cells in 200 µl of medium alone, and MR is maximum release, obtained by adding 100 µl 0.3% Triton X-100 to target cells.

Those mononuclear blood samples which showed high CTL activity were expanded and cloned via limiting dilution, and were screened again, using the same methodology. A first CTL clone was then isolated. The clone is referred to as 263/17 hereafter. A second CTL clone, 361A/17, was obtained similarly from the same experiment and was used as described further below when CTL 263/17 failed to grow indefinitley.

CTL clones 263/17 and 361A/17 were capable of lysing specifically the autologous tumor cells and not NK-target K562 cells. NK - target K562 cells are available from the ATCC, Rockville, Maryland.

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CTL clone 263/17 produced TNF when stimulated with the autologous tumor cells. To identify the HLA molecule that presented the antigen to CTL clone 263/17, inhibition experiments were carried out where the production of TNF was tested in the presence of monoclonal antibodies directed against HLA molecules or against CD4/CD8 accessory molecules. Four monoclonal antibodies were found to inhibit the production of TNF by CTL 263/17: (1) monoclonal antibody W6/32, which is directed against all HLA class I molecules (Parham et al., 1979, J. Immunol., 123:342); (2) antibody B1.23.2 which recognizes HLA-B and C molecules (Rebai et al., 1983, Tissue Antigens, 22:107); (3) antibody ME-1 which specifically recognizes HLA-B7 (Ellis et al., 1982, Hum. Immunol., 5:49); and (4) antibody B9.4.1 against CD8. No inhibition was found with antibodies directed against HLA Class II DR molecules (L243: Lampson et al., 1980, J. Immunol., 125:293), against HLA-A3 (GAPA 3: Berger et al., 1982 Hybridoma, 1:87) or against CD4 (13B.8.82). The conclusion was that CTL 263/17 was of the CD8 type, and recognized an antigen presented by HLA-B7.

To define the tumor specificity of this CTL clone, normal kidney cells derived from another patient which are also HLA-B7 (PTEC-HLA-B7 cells) were tested. These cells derive from the proximal tubular epithelium which is the site of origin of renal cell carcinoma. PTEC-HLA-B7 cells were not lysed by the CTL, suggesting that the antigen is specifically expressed on tumors.

Renal cell carcinoma line MZ-1851, which is derived from another HLA-B7 patient, was also lysed by the CTL, showing that the antigen is shared by independent tumors.

EXAMPLE 2: Isolation of a cDNA clone that directs the expression of the antigen recognized by CTL 263/17

A. cDNA library

RNA was isolated from LE-9211-RCC, and poly-A$^+$ RNA was purified by oligo-dT binding. cDNA was prepared by reverse transcription with an oligo-dT primer containing a *Not* I site, followed by second strand synthesis (Superscript Choice System, BRL, Life Technologies). The cDNA was then ligated to a *BstX* I adaptor, digested with *Not* I, size-fractionated (Sephacryl S-500 HR columns, BRL, Life Technologies) and cloned unidirectionally into the *BstX* I and *Not* I sites of pcDNA-I-Amp (Invitrogen). The recombinant plasmid was then electroporated into DH5α *E. coli* bacteria. 1500 pools of 100 recombinant bacteria were amplified and plasmid DNA of each pool was extracted by alkaline lysis, potassium acetate precipitation and phenol extraction.

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B. Transfection of COS cells

Plasmid DNA from the different pools was co-transfected into COS cells with 60 ng of the HLA-B7 cDNA (cloned by PCR from the cDNA of another HLA-B7 patient and inserted into plasmid vector pcDSRalpha). The transfection was made in duplicate wells. Briefly, samples of COS-7 cells were seeded, at 15,000 cells/well into tissue culture flat bottom microwells, in DMEM supplemented with 10% fetal calf serum. The cells were incubated overnight at 37°C, medium was removed and then replaced by 50 µl/well of DMEM medium containing 10% Nu-Serum (Collaborative Research, Bedford, MA), 400µg/ml DEAE-dextran, and 100 µM chloroquine, plus 100 ng of the plasmids. Following four hours of incubation at 37°C, the medium was removed, and replaced by 50 µl of PBS containing 10% dimethyl sulfoxide (DMSO). This medium was removed after two minutes and replaced by 200 µl of DMEM supplemented with 10% FCS.

Following this change in medium, COS cells were incubated for 24-48 hours at 37°C. The transfectants then were screened with CTL 263/17. After first removing the medium, 3000 CTL 263/17 cells were added to each well in 100µl of medium containing 25 U/ml IL-2. The amount of TNF present in the supernatant was then measured by testing its cytotoxicity for WEHI 164.13 cells. Most pools gave a TNF concentration below 10 pg/ml. Two pools (1157 and 1319) gave higher concentrations in both of the duplicate wells (24 to 37 pg/ml). The bacteria of pool 1319 were cloned and 1200 clones were obtained. Their plasmid DNA was extracted and transfected into COS cells with HLA-B7. The transfectants were screened with CTL 263/17. One cDNA clone (9H3) gave a high TNF production by CTL 263/17. Figure 1 shows the result obtained when this cDNA (60 ng) was transfected into COS cells with the HLA-B7 cDNA (60 ng) and screened with CTL 263/17.

This cDNA also was stably transfected into LB23-SAR cells, an HLA-B7 sarcoma line. The lysis test then was performed with CTL clone 361A/17, which recognizes the same antigen as CTL clone 263/17. These stably transfected cells were recognized in the same manner as the COS-HLA-B7-cDNA 9H3 cells.

EXAMPLE 3: Sequence of cDNA 9H3

cDNA clone 9H3 is 1130 bp long. This cDNA was not complete because its size was smaller than that of an mRNA observed on a Northern blot (1.6kb). The 5' end of the cDNA was cloned by RACE-PCR and the entire sequence was confirmed. This entire sequence is shown as SEQ.ID.NO.1. A comparison with the sequences reported in databanks showed at the 3' end a high homology with a short sequence of 235 bp called "expressed sequence tag", whose function is unknown (1), and at the 5' end a limited homology (75% in a stretch of 95 bases) with the antisense strand of two human endogenous retroviruses called RTVL-H2 and RGH2 (2, 3).

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The gene was called RAGE, for Renal tumor AntiGEn.

The sequence contains five open reading frames, ORF1: 99 base pairs encoding a protein of 32 residues; ORF2: 123 base pairs encoding a protein of 40 residues; ORF3: 87 base pairs encoding a protein of 28 residues; ORF4: 288 base pairs encoding a protein of 95 residues; and ORF5: 222 base pairs encoding a protein of 73 residues. (SEQ.ID.NOs.2, 4, 6, 8 and 10, respectively). SEQ.ID.NO.4 codes for the TRAP from which the antigenic peptide reactive with CTL 263/17 (as an HLA-B7/peptide complex) is derived.

EXAMPLE 4: Identification of Additional RAGE Genes

This example describes the identification of three additional RAGE genes and the determination that only the RAGE gene identified in the above examples, now designated RAGE-1, encodes a RAGE TRA reactive with CTL 263/17.

A probe was prepared from RAGE-1 cDNA and used to screen a LE9211-RCC cDNA library for additional RAGE genes. Three cDNAs homologous to RAGE, labeled RAGE-2 (SEQ.ID.NO.12), RAGE-3 (SEQ.ID.NO.13) and RAGE-4 (SEQ.ID.NO.14), were isolated. The RAGE-2, 3 and 4 genes were sequenced by standard methods. Comparison of the nucleotide sequences of these RAGE cDNAs with the RAGE-1 cDNA showed that truncated and novel open reading frames (ORFs) were present in the newly identified RAGE cDNAs. RAGE-2, RAGE-3 and RAGE-4 contained an insert of 37 bp at position 249 of RAGE1 (within the sequence corresponding to ORF2 (SEQ.ID.NO.4) of RAGE-1). For the RAGE-2 cDNA, comparison with the cosmid sequence indicated that this insertion corresponds to the beginning of an exon. Its absence from the RAGE-1 cDNA might result from the use of an alternative downstream acceptor site. In addition, RAGE-2, 3 and 4 differ from RAGE-1 in lacking a nucleotide at position 192 of RAGE-1. These changes significantly modify the ORFs of RAGE-2, 3 and 4 that are homologous to ORF2 and 3 of RAGE-1. In addition, RAGE-3 has another insertion of 47 bp at the 5' end. Except for these differences, the RAGE-1, 2 and 3 sequences are identical.

RAGE-4 is about 800 bp longer than the other RAGE cDNAs. Its 5' sequence is identical to that of RAGE-2, but from position 434 to the poly-A tail, the RAGE-4 sequence differs totally from the other RAGE cDNAs. The RAGE-4 cDNA was shown not to be chimeric. The starting position of the 3' unrelated sequence corresponds to an exon-intron boundry in the RAGE genomic sequence, and the 3' unrelated sequence was present in the 3' end of the RAGE gene. Therefore, the RAGE-4 cDNA appears to result from differential splicing of the RAGE-2 gene. The schematic alignment of the four cDNAs is shown in Fig. 2. There are 17 ORFs in the four RAGE cDNAs. Of these 17, 10 are different. The ORFs are as follows:

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Gene	ORF	Nucleotide No.	SEQ.ID.NO.
RAGE-1	ORF1	173-271	2
	ORF2	204-326	4
	ORF3	313-399	6
	ORF4	323-610	8
	ORF5	444-665	10
RAGE-2	ORF2'	217-276	15
	ORF3'	273-449	17
	ORF4	373-660	19
	ORF5	494-715	21
RAGE-3	ORF6	185-247	23
	ORF2'	274-333	25
	ORF3'	330-506	27
	ORF4	430-717	29
	ORF5	551-772	31
RAGE-4	ORF2'	213-272	33
	ORF3"	269-832	35
	ORF4'	369-557	37

The RAGE-2 . RAGE-3 and RAGE-4 cDNAs were cloned into expression plasmids by art-standard procedures and transfected as described with HLA-B7 into COS-7 cells to determine if these cDNAs also encoded the antigen recognized by CTL 263/17. Parallel control experiments with the RAGE cDNA (now referred to as RAGE-1) and with LE9211-RCC cells were also performed.

Incubation of LE9211-RCC cells or COS-7 cells cotransfected with RAGE-1 and HLA-B7 with CTL 263/17 strongly induced release of TNF by CTL 263/17. Cotransfection of RAGE-2. RAGE-3 or RAGE-4 and HLA-B7 did not elicit TNF release. Therefore. only RAGE-1 was able to transfer expression of the antigen recognized by CTL 263/17.

EXAMPLE 5: Identification of ORF containing RAGE tumor rejection antigen

The 37 bp insertion in RAGE-2. 3 and 4 caused premature termination of ORF2 in these three genes. It was reasoned. therefore. that the antigenic peptide recognized by CTL 263/17 was encoded by the 3' end of ORF2. To test this hypothesis. the DNA sequences corresponding to ORF2 of RAGE 1 and ORF2' of RAGE-2 and RAGE-3 were cloned into an expression vector and transfected into COS-7 cells with HLA-B7 as described above. As positive controls. the RAGE-1 cDNA was cotransfected with HLA-B7 into COS-7 cells or LE2911-RCC cells were used. These transfectants or LE2911-RCC cells were used to provoke release of TNF from CTL 263/17 cells. Among the ORF transfectants. only the ORF2 from

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RAGE-1 successfully stimulated TNF release from CTL 263/17 cells (Fig. 3). This experiment confirmed that the RAGE antigenic peptide recognized by CTL 263/17 cells was encoded by the 3' end of ORF2 of RAGE-1.

EXAMPLE 6: Identification of RAGE tumor rejection antigen peptide

Synthetic peptides corresponding to the 3' end of RAGE-1 ORF2 were synthesized and tested for stimulation of TNF release from CTL 263/17 cells. COS-7 cells were transfected with HLA-B7 as described above and a synthetic peptide corresponding to a 3' portion of ORF2 was added to the culture. CTL 263/17 cells were added and the production of TNF was measured after 18 hours (Fig. 4). Peptide SPSSNRIRNTST (SEQ.ID.NO.39) efficiently stimulated the release of TNF from CTL 263/17. Since peptides presented by HLA class I molecules are usually 9 amino acids in length, we tested nonameric peptides (SEQ.ID.NOs. 40, 41 and 42) derived from the dodecameric peptide (SEQ.ID.NO.39) previously used to stimulate TNF release from CTL 263/17 cells. The results of these experiments are shown in Fig. 4. One of these peptides (SPSSNRIRN, SEQ.ID.NO.40) was recognized by CTL 263/17, but to a far lesser extent than the dodecameric peptide, which suggested that the nonamer (SEQ.ID.NO.40) was not the optimal peptide. The decameric peptide (SPSSNRIRNT, SEQ.ID.NO.43) was very efficiently recognized by CTL 263/17.

EXAMPLE 7: Activity of RAGE tumor rejection antigen nonamer and decamer peptides

This example shows the ability of the RAGE TRA peptide to induce lysis of HLA-B7-expressing cells and the relative efficiencies of the nonamer and decamer peptides.

Nonameric and decameric RAGE peptides (SEQ.ID.NOs. 40 and 43, respectively) were tested for the ability to induce cell lysis of HLA-B7$^+$ LB23-EBV B cells by CTL 263/17 cells in a dose response assay. Lyophilized peptides were dissolved at 20 mg/ml in DMSO, then diluted to 2 mg/ml in 10mM acetic acid and stored at -80°C. Target cells, HLA-B7$^+$ EBV-transformed lymphoblastoid cells (LB23-EBV cells), were labeled with ^{51}Cr, as described above, for 1 hour at 37°C followed by extensive washing to remove unincorporated label. LB23-EBV cells were then incubated in 96-well microplates in the presence of various concentrations of peptides for 30 minutes at 37°C. CTL263/17 were then added in an equal volume of medium at an effector:target ratio of 10:1. Chromium-51 release was measured after 4 hours. Fig. 5 shows the results of the dose response assay. Half maximal lysis of LB23-EBV cells was induced at a concentration of 30 ng/ml SPSSNRIRNT peptide (SEQ.ID.NO.43).

EXAMPLE 8: Expression of RAGE-1 gene

The expression of RAGE was tested by PCR using the following primers:

SEQ.ID.NO.46

- GTG TCT CCT TCG TCT CTA CTA (sense primer)

SEQ.ID.NO.47

- GGT GTG CCG ATG ACA TCG (antisense primer common to all RAGE genes)

SEQ.ID.NO.48

- GAG GTA TTC CTG ATC CTG (antisense primer specific for RAGE-1)

First, total RNA was taken from the particular sample, using art recognized techniques. This RNA was used to prepare cDNA. The protocol used to make the cDNA involved combining 4 µl of 5x reverse transcriptase buffer, 1 µl of each dNTP (10mM), 2 µl of dithiothreitol (100mM), 2 µl of dT-15 primer (20 µM), 0.5 µl of RNasin (40 units/µl), and 1 µl of M-MLV reverse transcriptase (200 units/µl). Next, 6.5 µl of template RNA (1 µg/3.25 µl water, or 2 µg total template RNA) was added. The total volume of the mixture was 20 µl. This was mixed and incubated at 42°C for 60 minutes, after which it was chilled on ice. A total of 80 µl of water was then added, to 100 µl total. This mixture was stored at -20°C until used in PCR.

The reagents for PCR included:

- 5 microliters of 10x DynaZyme buffer
- 20 pmoles of each primer
- 5 nanomoles of each dNTP
- 1 unit of polymerizing enzyme "Dynazyme" (2 units/µl)
- 5 µl of cDNA (corresponding to 100 ng total RNA)
- water to a final volume of 50 µl

The mixture was combined, and layered with one drop of mineral oil. The mixture was transferred to a thermocycler block, preheated to 94°C, and amplification was carried out for one cycle of 15 min at 94°C, followed by 33 cycles of:

- 1 min. at 94°C
- 2 min. at 56°C or 60°C (see below)
- 3 min. at 72°C

A final extension step of 15 min. was then performed at 72°C. Expression of all RAGE genes was tested by PCR amplification with pan-RAGE sense (SEQ.ID.NO.46) and antisense (SEQ.ID.NO.47) primers using an annealing step of 60°C for 2 minutes. Expression of only RAGE-1 gene was tested by PCR amplification with pan-RAGE sense (SEQ.ID.NO.46) and RAGE-1-specific antisense (SEQ.ID.NO.48) primers using an

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annealing step of 56°C for 2 minutes. The PCR product of 194 base pairs (general to all RAGE genes tested) and 239 base pairs (specific for RAGE-1 genes) were visualized on an agarose gel (1.5%) containing ethidium bromide.

The gene was found to be tumor-specific. The gene was silent in all normal tissues tested, except for retina. In particular, the gene was silent in adrenals, bladder, bone marrow, brain, breast, cerebellum, colon, heart, kidney, liver, lung, melanocytes, muscle, nevus, ovary, placenta, prostate, skin, splenocytes, stomach, testis, thymocytes, uterus and healing wounds. The gene, however, was found to be expressed in a variety of tumor cell lines and tumor tissue samples (Table 1). It is also expressed in some other tumors which are not listed here, although not frequently.

Table 1. Expression of RAGE-1 Gene in Tumor Samples

Histological Type	Number of Tumors Expressing	
	ALL RAGE	RAGE-1
Tumor Samples		
Renal carcinoma	2/57	1/57
Sarcomas	5/25	3/25
Bladder tumors	superficial -0/29 infiltrating -3/37	0/29 3/37
Melanomas	primary lesions -2/60 metastases -8/177	2/60 6/177
Head and neck tumors	2/50	1/50
Mammary carcinomas	3/128	1/128
Prostatic carcinomas	0/22	0/22
Colorectal carcinomas	0/48	0/48
Leukemias	0/19	0/19
Lung carcinomas (NSCLC[1]) (SCLC)	0/59 0/5	0/59 0/5
Mesotheliomas	1/3	0/3
Brain tumors	0/11	0/11
Oesophage tumors	0/7	0/7
Ovarian tumors	0/3	0/3
Tumor Cell Lines		
Renal carcinoma	8/19	7/19
Bladder tumors	3/3	3/3
Mesotheliomas	11/19	8/19

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Head and neck tumors	3/7	1/7
Sarcomas	2/6	1/6
Melanomas	11/78	7/78
Colorectal carcinomas	1/17	1/17
Lung carcinomas (NSCLC[1]) (SCLC)	0/2 0/26	0/2 0/26
Leukemias/Lymphomas	0/11	0/11
Brain tumors	0/1	0/1
Gastric tumors	0/2	0/2

[1] NSCLC: non-small cell lung carcinoma.

The foregoing examples show the isolation of a nucleic acid molecule which codes for a TRAP. This TRAP coding molecule, however, is not homologous with any of the previously disclosed coding sequences described in the references set forth *supra*. Hence, one aspect of the invention is an isolated nucleic acid molecule which includes all or a unique portion of the nucleotide sequence set forth in SEQ.ID.NO.1, SEQ.ID.NO.4, SEQ.ID.NO.6 or SEQ.ID.NO.10. It is also expected that antigens derived from other RAGE ORFs encoded by SEQ.ID.NOs. 12, 13 and 14 may be recognized cytolytic T lymphocyte clones other than CTL263/17. Thus, the invention in another aspect involves any one or more of the RAGE family of genes, including isolated unique portions thereof such as portions encoding TRAPs and TRAs. RAGE TRAPs and TRAs derived therefrom and all of the diagnostic and therapeutic modalities relating thereto. The foregoing sequences are not MAGE, BAGE or GAGE sequences, as will be seen by comparing them to the MAGE, BAGE or GAGE sequences described in the references.

Also a part of the invention are those nucleic acid sequences which also code for a non-MAGE, non-BAGE and non-GAGE tumor rejection antigen precursor but which hybridize to a nucleic acid molecule consisting of the above described nucleotide sequences, under stringent conditions. The term "stringent conditions" as used herein refers to parameters with which the art is familiar. More specifically, stringent conditions, as used herein, refers to hybridization at 65°C in hybridization buffer (3.5 x SSC, 0.02% Ficoll, 0.02% Polyvinyl pyrolidone, 0.02% Bovine Serum Albumin, 25mM NaH_2PO_4 (pH7), 0.5% SDS, 2mM EDTA). SSC is 0.15M Sodium Chloride/0.15M Sodium Citrate, pH 7; SDS is Sodium dodecyl Sulphate; and EDTA is Ethylene diamine tetra acetic acid. After hybridization, the membrane upon which the DNA is transferred is washed at 2xSSC at room temperature and then at 0.1xSSC/0.1xSDS at 65°C.

There are other conditions, reagents, and so forth which can be used, which result in the same degree of stringency. The skilled artisan will be familiar with such conditions, and thus they are not given here. The

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skilled artisan also is familiar with the methodology for screening cells, preferably cancer cells, for expression of such molecules which then are routinely isolated, followed by isolation of the pertinent nucleic acid.

In screening for RAGE family members, a Southern blot may be performed using the foregoing conditions, together with a ^{32}P probe. After washing the membrane to which the DNA was finally transferred, the membrane can be placed against X-ray film to detect the radioactive signal.

The invention thus provides isolated unique fragments of SEQ.ID.NO.1 or its complement. A unique fragment is one that is a 'signature' for RAGE genes. It, for example, is long enough to assure that its precise sequence is not found in molecules outside of the RAGE family as defined by claim 23. Preferred unique fragments are those found only in ORF2 or its complement. Unique fragments can be used as probes in Southern blot assays to identify RAGE family members including those expressing ORF2 or can be used in amplification assays such as those employing PCR. As known to those skilled in the art, large probes such as 200 bp or more are preferred for certain uses such as Southern blots, while smaller fragments will be preferred for uses such as PCR. As will be recognized by those skilled in the art, the size of a unique fragment will depend upon its conservency in the genetic code. Thus, some regions of SEQ.ID.NO.1, SEQ.ID.NO.12, SEQ.ID.NO.13 and SEQ.ID.NO.14 will require longer segments to be unique while others will require only short segments, typically between 12 and 32 bp (e.g. 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31 and/or 32 bases long). Virtually any segment of SEQ.ID.NO.1 that is 18 or more nucleotides in length will be unique. Those skilled in the art are well versed in methods for selecting such sequences, typically on the basis of the ability of the unique fragment to selectively distinguish the sequence of interest from nonfamily members. A comparison of the sequence of the fragment to those on known data bases typically is all that is necessary, although *in vitro* confirmatory hybridization and sequencing analysis may be performed.

For any pair of PCR primers constructed and arranged to selectively amplify RAGE-1, a RAGE-1 specific primer may be used. Such a primer is a contiguous stretch of RAGE-1 which hybridizes to both sides of the insertion point in ORF2 which is altered by the insertion of additional nucleotides in other RAGE genes. Such a specific primer would fully hybridize to a contiguous stretch of nucleotides only in RAGE-1, but would hybridize only in part to RAGE genes that do not share ORF 2. For efficient PCR priming and RAGE 1 identification, the RAGE 1 specific primer should be constructed and arranged so it does not hybridize efficiently at its 3' end to RAGE genes other than RAGE 1. To accomplish this, the primer can be described as having two ends: a 5' end that is contiguous with and complementary to one side of the insertion point joined directly to a 3' end that is contiguous with and complementary to the opposite side of the insertion point. By making the 5' end of the primer substantially longer than the 3' end, and by making the 3' end short

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(i.e. 1-4 nucleotides), then the kinetics of hybridization will strongly favor hybridization at the 5' end. In this instance, 3' initiated PCR extension will occur only when both the 5' and 3' ends hybridize to the nucleic acid. i.e. only when ORF 2 is present without an insert.

RAGE-1 specific primers, as described above, may be designed to prime DNA synthesis on either strand of the DNA helix, described herein as the Watson or the Crick strands. The sequence in RAGE 1 which flanks the insertion point, is 5'-CAAACANGGATCA-3' (SEQ.ID.NO.49; Watson strand, N is a nucleotide insert). A RAGE-1 specific primer designed to preferentially amplify the Watson strand of RAGE-1 typically would comprise 12 and preferably 15 or more nucleotides ary to the nucleotides of the Watson strand 3' to the insertion point. The remaining portion of the primer would be one to four nucleotides long and would be complementary to the sequence 5' to the insertion point. Such a primer would be perfectly complementary and contiguous with its complement in RAGE-1. The 3' end of the primer would hybridize to its complement in the Watson strand and initiate extension. In RAGE genes other than RAGE-1, the insertion of noncomplementary nucleotides at the insertion point of ORF2 would substantially eliminate hybridization of the 3' end of the RAGE-1 specific primer to the Watson strand 5' of the insert. The mismatch generated at the 3' end of the primer when hybridized to RAGE genes, other than RAGE-1, would preclude efficient amplification of those genes. Exemplary primers consist essentially of the following sequences, wherein N is zero, one or more contiguous nucleotides on the appropriate Watson or Crick strands:

5'-NTATTCCTGATCCT-3'(SEQ.ID.NO. 50);
5'-NTATTCCTGATCCTG-3'(SEQ.ID.NO. 51);
5'-NTATTCCTGATCCTGT-3'(SEQ.ID.NO. 52);
5'-NTATTCCTGATCCTGTT-3'(SEQ.ID.NO. 53);
5'-NCAAGTTCAAACAG-3'(SEQ.ID.NO. 54);
5'-NCAAGTTCAAACAGG-3'(SEQ.ID.NO. 55);
5'-NCAAGTTCAAACAGGA-3'(SEQ.ID.NO. 56); and
5'-NCAAGTTCAAACAGGAT-3'(SEQ.ID.NO. 57).

The expression of RAGE-1 may also be detected by PCR using primers which initiate extension on opposite sides of the insertion point. Analysis of amplification products can distinguish RAGE-1 amplification products from non-RAGE-1 amplification products by the length of the amplification products. Because the RAGE-1 gene does not contain the insert present in other RAGE genes, amplification products derived from RAGE-1 will be shorter than amplification products derived from other RAGE genes (by about

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37 base pairs). This difference may be distinguished readily using standard methods in the art. Additional methods which can distinguish nucleotide sequences of substantial homology, such as ligase chain rection ("LCR") and other methods, will be apparent to skilled artisans. RAGE 2, 3 and 4 specific primers may be prepared in a like manner.

The invention also includes the use of nucleic acid sequences which include alternative codons that encode the same amino acid residues as encoded by the RAGE genes. For example, as disclosed above in Example 7, a decameric peptide SPSSNRIRNT (SEQ.ID.NO.43) is a RAGE tumor rejection antigen. The serine residues (amino acids No. 1, 3 and 4 of SEQ.ID.NO.40) for example, are encoded by the codons TCA, AGT and TCA, respectively. In addition to TCA and AGT, serine amino acid residues may also be encoded by the codons TCC, TCG, TCT and AGC. Each of the six codons is equivalent for the purposes of encoding a serine residue. Thus, it will be apparent to one of ordinary skill in the art that any of the serine-encoding nucleotide triplets may be employed to direct the protein synthesis apparatus, *in vitro* or *in vivo*, to incorporate a serine residue. Similarly, nucleotide sequence triplets which encode other amino acid residues comprising a RAGE tumor rejection antigen include: CCA, CCC, CCG and CCT (proline codons); CGA, CGC, CGG, CGT, AGA and AGG (arginine codons); ACA, ACC, ACG and ACT (threonine codons); AAC and AAT (asparagine codons); and ATA, ATC and ATT (isoleucine codons). Other amino acid residues may be encoded similarly by multiple nucleotide sequences. Thus, the invention embraces degenerate nucleic acids that differ from the biologically isolated nucleic acids in codon sequence due to the degeneracy of the genetic code.

The examples above also show the isolation of peptides which are RAGE TRAs. These exemplary peptides are processed translation products of the nucleic acids of SEQ.ID.NO.1. As such, it will be appreciated by one of ordinary skill in the art that the translation products from which a RAGE TRA is processed to a final form for presentation may be of any length or sequence so long as they encompass the RAGE TRA. As demonstrated in the examples above, peptides or proteins as small as 9, 10, or 12 amino acids and as large as the amino acid sequence encoded by ORF1 are appropriately processed, presented by HLA-B7 and recognized by CTL263/17. The peptide of SEQ.ID.NO.23 may have one, two, three, four, five, six, seven, eight, nine, ten, or more amino acids added to either or both ends. The antigenic portion of such a peptide is cleaved out under physiological conditions for presentation by HLA class I molecules.

The amino acid sequence of proteins and peptides from which RAGE TRAs are derived may be of natural or non-natural origin, that is, they may comprise a natural RAGE TRAP molecule or may comprise a modified sequence as long as the amino acid sequence retains the tumor rejection antigen sequence recognized by the CTL when presented on the surface of a cell. For example, RAGE tumor rejection

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antigens in this context may be fusion proteins of a RAGE tumor rejection antigen and unrelated amino acid sequences, the translated polypeptide of ORF2 of the RAGE-1 gene, synthetic peptides of amino acid sequences shown in SEQ.ID.NOs.39, 40 and 43, labeled peptides, peptides isolated from patients with renal cell carcinoma, peptides isolated from cultured cells which express RAGE-1, peptides coupled to nonpeptide molecules for example in certain drug delivery systems and other molecules which include the amino acid sequence of SEQ.ID.NO.40.

It will also be seen from the examples that the invention embraces the use of the sequences in expression vectors, as well as to transfect host cells and cell lines, be these prokaryotic (e.g., *E. coli*), or eukaryotic (e.g., CHO cells, COS cells, yeast expression systems and recombinant baculovirus expression in insect cells). The expression vectors require that the pertinent sequence, i.e., those described *supra*, be operably linked to a promoter. As it has been found that human HLA-B7 presents a TRA derived from these genes, the expression vector may also include a nucleic acid sequence coding for HLA-B7. In a situation where the vector contains both coding sequences, it can be used to transfect a cell which does not normally express either one. The TRAP or TRA coding sequence may be used alone, when, e.g. the host cell already expresses HLA-B7. Of course, there is no limit on the particular host cell which can be used. As the vectors which contain the two coding sequences may be used in HLA-B7 presenting cells if desired, and the nucleic acid coding for the TRAP or TRA can be used in host cells which do not express HLA-B7.

The invention also embraces so-called expression kits, which allow the artisan to prepare a desired expression vector or vectors. Such expression kits include at least separate portions of at least two of the previously discussed materials. Other components may be added, as desired.

To distinguish the nucleic acid molecules and the TRAPs of the invention from the previously described MAGE family, BAGE gene and GAGE gene, the invention shall be referred to as the RAGE family of genes and TRAPs. Hence, whenever "RAGE" is used herein, specifically excluded are MAGE, BAGE and GAGE genes, gene products, TRAPs and TRAs.

The invention as described herein has a number of uses, some of which are described herein. First, the invention permits the artisan to diagnose a disorder characterized by expression of the TRAP. These methods involve determining expression of the TRAP gene, and/or TRAs derived therefrom, such as a TRA presented by HLA-B7. In the former situation, such determinations can be carried out via any standard nucleic acid determination assay, including the polymerase chain reaction, or assaying with labeled hybridization probes. In the latter situation, assaying with binding partners for complexes of TRA and HLA, such as antibodies, is especially preferred. An alternate method for determination is a TNF release assay, of the type described *supra*.

The isolation of the TRAP gene also makes it possible to isolate the TRAP molecule itself, and/or TRAs derived therefrom, especially TRAP and/or TRA molecules containing the amino acid sequences coded for by SEQ.ID.NO.1 or 4. Other TRAPs or TRAs encoded by SEQ.ID.NOs. 1, 12, 13 and 14 and recognized by other CTL clones and/or presented by other HLA molecules may be isolated by the procedures detailed herein. (There are numerous HLA molecules known to those skilled in the art, including but not limited to, those encoded by HLA-A, HLA-B, HLA-C, HLA-E, HLA-F and HLA-G genes.) A variety of methodologies well-known to the skilled practitioner can be utilized to obtain isolated TRAP molecules, and/or TRAs derived therefrom. The protein may be purified from cells which naturally produce the protein. Alternatively, an expression vector may be introduced into cells to cause production of the protein. In another method, mRNA transcripts may be microinjected or otherwise introduced into cells to cause production of the encoded protein. Translation of mRNA in cell-free extracts such as the reticulocyte lysate system also may be used to produce protein. Peptides comprising TRAs of the invention may also be synthesized *in vitro*. Those skilled in the art also can readily follow known methods for isolating proteins in order to obtain isolated TRAP and/or TRAs derived therefrom. These include, but are not limited to, immunochromotography, HPLC, size-exclusion chromatography, ion-exchange chromatography and immune-affinity chromatography. These isolated molecules when processed and presented as the TRA, or as complexes of TRA and HLA, such as HLA-B7, may be combined with materials such as adjuvants to produce vaccines useful in treating disorders characterized by expression of the TRAP molecule. In addition, vaccines can be prepared from cells which present the TRA/HLA complexes on their surface, such as non-proliferative cancer cells, non-proliferative transfectants, etcetera. In all cases where cells are used as a vaccine, these can be cells transfected with coding sequences for one or both of the components necessary to provoke a CTL response, or be cells which already express both molecules without the need for transfection. Vaccines also encompass naked DNA or RNA, encoding a RAGE TRA or precursor thereof, which may be produced *in vitro* and administered via injection, particle bombardment, nasal aspiration and other methods. Vaccines of the "naked nucleic acid" type have been demonstrated to provoke an immunological response including generation of CTLs specific for the peptide encoded by the naked nucleic acid (Science 259:1745-1748, 1993).

The TRAP molecule, its associated TRAs, as well as complexes of TRA and HLA, may be used to produce antibodies, using standard techniques well known to the art. Standard reference works setting forth the general principles of antibody production include Catty, D., Antibodies, A Practical Approach, Vol. 1, IRL Press, Washington DC (1988); Klein, J., Immunology: The Science of Cell-Non-Cell Discrimination, John Wiley and Sons, New York (1982); Kennett, R., et al., Monoclonal Antibodies, Hybridoma, A New Dimension In Biological Analyses, Plenum Press, New York (1980); Campbell, A., Monoclonal Antibody

Technology, in Laboratory Techniques and Biochemistry and Molecular Biology, Vol. 13 (Burdon, R. et al. EDS.). Elsevier Amsterdam (1984); and Eisen. H.N., Microbiology, third edition, Davis. B.D. et al. EDS. (Harper & Rowe, Philadelphia (1980).

The antibodies of the present invention thus are prepared by any of a variety of methods, including administering protein, fragments of protein, cells expressing the protein or fragments thereof and the like to an animal to induce polyclonal antibodies. The production of monoclonal antibodies is according to techniques well known in the art. As detailed herein, such antibodies may be used for example to identify tissues expressing protein or to purify protein. Antibodies also may be coupled to specific labeling agents for imaging or to antitumor agents, including, but not limited to, methotrexate, radioiodinated compounds, toxins such as ricin, other cytostatic or cytolytic drugs, and so forth. Antibodies prepared according to the invention also preferably are specific for the TRA/HLA complexes described herein.

When "disorder" is used herein, it refers to any pathological condition where the tumor rejection antigen precursor is expressed. An example of such a disorder is cancer, renal cell carcinoma in particular.

Some therapeutic approaches based upon the disclosure are premised on a response by a subject's immune system, leading to lysis of TRA presenting cells, such as HLA-B7 cells. One such approach is the administration of autologous CTLs specific to the complex to a subject with abnormal cells of the phenotype at issue. It is within the skill of the artisan to develop such CTLs *in vitro*. Generally, a sample of cells taken from a subject, such as blood cells, are contacted with a cell presenting the complex and capable of provoking CTLs to proliferate. The target cell can be a transfectant, such as a COS cell of the type described *supra*. These transfectants present the desired complex of their surface and, when combined with a CTL of interest, stimulate its proliferation. COS cells, such as those used herein are widely available, as are other suitable host cells. Specific production of a CTL clone has been described above. The clonally expanded autologous CTLs then are administered to the subject. Other CTLs specific to RAGE-1 and CTLs specific to RAGE TRAs encoded by RAGE-2, 3, or 4 may be isolated and administered by similar methods.

To detail a therapeutic methodology, referred to as adoptive transfer (Greenberg, J. Immunol. 136(5): 1917 (1986); Riddel et al., Science 257: 238 (7-10-92); Lynch et al. Eur. J. Immunol. 21: 1403-1410 (1991); Kast et al., Cell 59: 603-614 (11-17-89)), cells presenting the desired complex are combined with CTLs leading to proliferation of the CTLs specific thereto. The proliferated CTLs are then administered to a subject with a cellular abnormality which is characterized by certain of the abnormal cells presenting the particular complex. The CTLs then lyse the abnormal cells, thereby achieving the desired therapeutic goal.

The foregoing therapy assumes that at least some of the subject's abnormal cells present the relevant HLA/TRA complex. This can be determined very easily, as the art is very familiar with methods for

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identifying cells which present a particular HLA molecule, as well as how to identify cells expressing DNA of the pertinent sequences, in this case a RAGE sequence. Once cells presenting the relevant complex are identified via the foregoing screening methodology, they can be combined with a sample from a patient, where the sample contains CTLs. If the complex presenting cells are lysed by the mixed CTL sample, then it can be assumed that a RAGE derived, TRA is being presented, and the subject is an appropriate candidate for the therapeutic approaches set forth *supra*.

Adoptive transfer is not the only form of therapy that is available in accordance with the invention. CTLs can also be provoked *in vivo*, using a number of approaches. One approach, i.e., the use of non-proliferative cells expressing the complex, has been elaborated upon *supra*. The cells used in this approach may be those that normally express the complex, such as irradiated tumor cells or cells transfected with one or both of the genes necessary for presentation of the complex. Chen et al., Proc. Natl. Acad. Sci. USA 88: 110-114 (January, 1991) exemplifies this approach, showing the use of transfected cells expressing HPVE7 peptides in a therapeutic regime. Various cell types may be used. Similarly, vectors carrying one or both of the genes of interest may be used. Viral or bacterial vectors are especially preferred. For example, nucleic acids which encode a RAGE TRA may be operably linked to promoter and enhancer sequences which direct expresion of the RAGE TRA in certain tissues or cell types. The nucleic acid may be incorporated into an expression vector. Expression vectors may be unmodified extrachromosomal nucleic acids, plasmids or viral genomes constructed or modified to enable insertion of exogenous nucleic acids, such as those encoding RAGE TRAs. Nucleic acids encoding a RAGE TRA also may be inserted into a retroviral genome, thereby facilitating integration of the nucleic acid into the genome of the target tissue or cell type. In these systems, the gene of interest is carried by a microorganism, e.g., a Vaccinia virus, retrovirus or the bacteria BCG, and the materials de facto "infect" host cells. The cells which result present the complex of interest, and are recognized by autologous CTLs, which then proliferate.

A similar effect can be achieved by combining the TRAP or a stimulatory fragment thereof with an adjuvant to facilitate incorporation into HLA-B7 presenting cells *in vivo*. The TRAP is processed to yield the peptide partner of the HLA molecule while the TRA is presented without the need for further processing. Generally, subjects can receive an intradermal injection of an effective amount of the RAGE TRAP, and/or TRAs derived therefrom. Initial doses can be followed by booster doses, following immunization protocols standard in the art.

As part of the immunization protocols, substances which potentiate the immune response may be administered with nucleic acid or peptide components of a cancer vaccine. Such immune response potentiating compound may be classified as either adjuvants or cytokines. Adjuvants may enhance the

immunological response by providing a reservoir of antigen (extracellularly or within macrophages), activating macrophages and stimulating specific sets of lymphocytes. Adjuvants of many kinds are well known in the art; specific examples include MPL (SmithKline Beecham), a congener obtained after purification and acid hydrolysis of *Salmonella minnesota* Re 595 lipopolysaccharide, QS21 (SmithKline Beecham), a pure QA-21 saponin purified from *Quillja saponaria* extract, and various water-in-oil emulsions prepared from biodegradable oils such as squalene and/or tocopherol. Cytokines are also useful in vaccination protocols as a result of lymphocyte stimulatory properties. Many cytokines useful for such purposes will be known to one of ordinary skill in the art, including interleukin-12 (IL-12) which has been shown to enhance the protective effects of vaccines (Science 268: 1432-1434, 1995).

When administered, the therapeutic compositions of the present invention are administered in pharmaceutically acceptable preparations. Such preparations may routinely contain pharmaceutically acceptable concentrations of salt, buffering agents, preservatives, compatible carriers, supplementary immune potentiating agents such as adjuvants and cytokines and optionally other therapeutic agents.

The preparations of the invention are administered in effective amounts. An effective amount is that amount of a pharmaceutical preparation that alone, or together with further doses, stimulates the desired response. In the case of treating cancer, the desired response is inhibiting the progression of the cancer. This may involve only slowing the progression of the disease temporarily, although more preferably, it involves halting the progression of the disease permanently. This can be monitored by routine methods or can be monitored according to diagnostic methods of the invention discussed herein.

Where it is desired to stimulate an immune response using a therapeutic composition of the invention, this may involve the stimulation of a humoral antibody response resulting in an increase in antibody titer in serum, a clonal expansion of cytotoxic lymphocytes, or some other desirable immunologic response. It is believed that doses of immunogens ranging from one nanogram/kilogram to 100 miligrams/kilogram, depending upon the mode of administration, would be effective. The preferred range is believed to be between 500 nanograms and 500 micrograms per kilogram. The absolute amount will depend upon a variety of factors, including the material selected for administration, whether the administration is in single or multiple doses, and individual patient parameters including age, physical condition, size, weight, and the stage of the disease. These factors are well known to those of ordinary skill in the art and can be addressed with no more than routine experimentation.

Other aspects of the invention will be clear to the skilled artisan and need not be repeated here.

The terms and expressions which have been employed are used as terms of description and not of limitation, and there is no intention in the use of such terms and expressions of excluding any equivalents of

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the features shown and described or portions thereof, it being recognized that various modifications are possible within the scope of the invention.

References

1) Gleser, L., and Swaroop, A. 1992. Expressed sequence tags and chromosomal localization of cDNA clones from a subtracted retinal pigment epithelium library. Genomics 13. 873-876.

2) Mager, D., and Freeman, J.D. 1987. Human endogenous retrovirus-like genome with Type C pol sequences and gag sequences related to human T-cell lymphotropic viruses. J. Virol. 61. 4060-4066.

3) Hirose, Y., Takamatsu, M., Harada, F. 1993. Presence of env genes in members of the RTVL-H family of human endogenous retrovirus-like elements. Virology 192. 52-61.

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Sequence Listing

(1) GENERAL INFORMATION:

(i) APPLICANT:

(A) NAME: LUDWIG INSTITUTE FOR CANCER RESEARCH

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(E) COUNTRY: UNITED STATES OF AMERICA

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(ii) TITLE OF INVENTION: RAGE TUMOR REJECTION ANTIGENS

(iii) NUMBER OF SEQUENCES: 57

(iv) CORRESPONDENCE ADDRESS:

(A) ADDRESSEE: WOLF, GREENFIELD & SACKS, P.C.

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(C) CITY: BOSTON

(D) STATE: MASSACHUSETTS

(E) COUNTRY: UNITED STATES OF AMERICA

(F) ZIP: 02210

(v) COMPUTER READABLE FORM:

(A) MEDIUM TYPE: Floppy disk

(B) COMPUTER: IBM PC compatible

(C) OPERATING SYSTEM: PC-DOS/MS-DOS

(D) SOFTWARE: PatentIn Release #1.0, Version #1.25

(vi) CURRENT APPLICATION DATA:

(A) APPLICATION NUMBER:

(B) FILING DATE:

(C) CLASSIFICATION:

(vii) PRIOR APPLICATION DATA:

(A) APPLICATION NUMBER: US 08/401,015

(B) FILING DATE: 21-MAR-1995

(vii) PRIOR APPLICATION DATA:

(A) APPLICATION NUMBER: US 08/530,569

(B) FILING DATE: 20-SEP-1995

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(C) REFERENCE/DOCKET NUMBER: L0461/7002WO

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(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1311 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Homo sapiens

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

GGTGAGCAGC CAAAGCAGGC ATCCCCGCAG TTGACTTGCC ACCAAGGGAA TGTGGGTGAA 60

TGACCAAGGC AGGCATCCTC GCGGTGATCA GACACCAATG GAGTGTGGGT GAATAATCAG 120

GCAGGCATCC CCGCAGTGAT TAAACACCAA GAGAAGACTA TTCCTGAGTC TGTGACTGGT 180

GCTGGAGTTT TGAGTCCACA GATAAAATGT GTCTCCTTCG TCTCTACTAG AGAGGAAAAA 240

GAACTGGAAT TGGAAGAACA GGGAGACTGA AGGGTAGCAA GAGAGGCTGG AGAAGAGAGT 300

GAAAAGACCG CTTACCTGAT TTGAAATTGT CTGCAGCCCC TCTTTCCTGG AGTAAATGAA 360

CTGGACCAAA TCTCAAAAAA TCCACGATGT CATCGGCACA CCCGCTCAGA AGATCCTCAC 420

CAAGTTCAAA CAGGATCAGG AATACCTCTA CTAACAACCA ATTTGTCCCC ACAATGCCTC 480

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TCCCTCCTGC ACGCAATGGT GGCCTATGAT CCCGATGAGA GAATCGCCGC CCACCAGGCC 540

CTGCAGCACC CCTACTTCCA AGAACAGAGA AACAGTCCCT AAAGCAAGAG GAGGACCGTC 600

CCAAGAGACG AGGACCGGCC TATGTCATGG AACTGCCCAA ACTAAAGCTT TCGGGAGTGG 660

TCAGACTGTC GTCTTACTCC AGCCCCACGC TGCAGTCCGT GCTTGGATCT GGAACAAATG 720

GAAGAGTGCC GGTGCTGAGA CCCTTGAAGT GCATCCCTGC GAGCAAGAAG ACAGATCCGC 780

AGAAGGACCT TAAGCCTGCC CCGCAGCAGT GTCGCCTGCC CACCATAGTG CGGAAAGGCG 840

GAAGATAACT GAGCAGCACC GTCGTCTCGA CTTCGGAGGC AACACCAAGC CCGACCGGGC 900

CAGGCCTGGG TGATCTGCTG CTGAGACGCC ACGGAGGGCT GGGGATGCGC CTGCGTCCGT 960

TTCGCGCTGG CCGGGGCTCT GGGTGCTGCC CTGCGCCCTG CCGCACCCGC GGCCCGCGCA 1020

GCTGCCTAGG ATGTTCTGGG CTAATATACT TGTAAAACCA CCGCATTCTA GGGTTTTCTT 1080

TCATTTTCGT TAAGAATTTG GGGCAGGAAA TACTTTGTAA CTTTGTATAT GAATCAAAAC 1140

AAACGAGCAG GCATTTCTGT GATGTGTTGG GCGTGGTTGG AAGGTGGGTT CTGCGTGTCC 1200

CTTCCCAGCG CTGCTGGTCA GTCGTGGAGC GCCATCATGT CTTACCAGTG ACGCTGCTGA 1260

CACCCCTGAC TTTTATTAAA GAATAAGCTG TCGTTAAAAA AAAAAAAAAA A 1311

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 99 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Homo sapiens

(ix) FEATURE:

(A) NAME/KEY: CDS

(B) LOCATION: 1..99

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

```
ATG AAC TGG ACC AAA TCT CAA AAA ATC CAC GAT GTC ATC GGC ACA CCC      48
Met Asn Trp Thr Lys Ser Gln Lys Ile His Asp Val Ile Gly Thr Pro
 1               5                  10                  15

GCT CAG AAG ATC CTC ACC AAG TTC AAA CAG GAT CAG GAA TAC CTC TAC      96
Ala Gln Lys Ile Leu Thr Lys Phe Lys Gln Asp Gln Glu Tyr Leu Tyr
            20                  25                  30

TAA                                                                  99
```

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 32 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

Met Asn Trp Thr Lys Ser Gln Lys Ile His Asp Val Ile Gly Thr Pro
1 5 10 15

Ala Gln Lys Ile Leu Thr Lys Phe Lys Gln Asp Gln Glu Tyr Leu Tyr
20 25 30

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 123 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

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(v) FRAGMENT TYPE: internal

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Homo sapiens

(ix) FEATURE:

(A) NAME/KEY: CDS

(B) LOCATION: 1..123

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

```
ATG TCA TCG GCA CAC CCG CTC AGA AGA TCC TCA CCA AGT TCA AAC AGG      48
Met Ser Ser Ala His Pro Leu Arg Arg Ser Ser Pro Ser Ser Asn Arg
 1               5                  10                  15

ATC AGG AAT ACC TCT ACT AAC AAC CAA TTT GTC CCC ACA ATG CCT CTC      96
Ile Arg Asn Thr Ser Thr Asn Asn Gln Phe Val Pro Thr Met Pro Leu
            20                  25                  30

CCT CCT GCA CGC AAT GGT GGC CTA TGA                                 123
Pro Pro Ala Arg Asn Gly Gly Leu
        35                  40
```

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 40 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

Met Ser Ser Ala His Pro Leu Arg Arg Ser Ser Pro Ser Ser Asn Arg
1 5 10 15

Ile Arg Asn Thr Ser Thr Asn Asn Gln Phe Val Pro Thr Met Pro Leu
20 25 30

Pro Pro Ala Arg Asn Gly Gly Leu
35 40

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(vi) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

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(ix) FEATURE:

(A) NAME/KEY: CDS

(B) LOCATION: 1..87

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

```
ATG GTG GCC TAT GAT CCC GAT GAG AGA ATC GCC GCC CAC CAG GCC CTG      48
Met Val Ala Tyr Asp Pro Asp Glu Arg Ile Ala Ala His Gln Ala Leu
 1               5                  10                  15

CAG CAC CCC TAC TTC CAA GAA CAG AGA AAC AGT CCC TAA                  87
Gln His Pro Tyr Phe Gln Glu Gln Arg Asn Ser Pro
            20                  25
```

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 28 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

```
Met Val Ala Tyr Asp Pro Asp Glu Arg Ile Ala Ala His Gln Ala Leu
 1               5                  10                  15

Gln His Pro Tyr Phe Gln Glu Gln Arg Asn Ser Pro
            20                  25
```

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 288 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Homo sapiens

(ix) FEATURE:

(A) NAME/KEY: CDS

(B) LOCATION: 1..288

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

```
ATG ATC CCG ATG AGA GAA TCG CCG CCC ACC AGG CCC TGC AGC ACC CCT        48
Met Ile Pro Met Arg Glu Ser Pro Pro Thr Arg Pro Cys Ser Thr Pro
 1               5                  10                  15

ACT TCC AAG AAC AGA GAA ACA GTC CCT AAA GCA AGA GGA GGA CCG TCC        96
```

Thr Ser Lys Asn Arg Glu Thr Val Pro Lys Ala Arg Gly Gly Pro Ser
20 25 30

CAA GAG ACG AGG ACC GGC CTA TGT CAT GGA ACT GCC CAA ACT AAA GCT 144
Gln Glu Thr Arg Thr Gly Leu Cys His Gly Thr Ala Gln Thr Lys Ala
35 40 45

TTC GGG AGT GGT CAG ACT GTC GTC TTA CTC CAG CCC CAC GCT GCA GTC 192
Phe Gly Ser Gly Gln Thr Val Val Leu Leu Gln Pro His Ala Ala Val
50 55 60

CGT GCT TGG ATC TGG AAC AAA TGG AAG AGT GCC GGT GCT GAG ACC CTT 240
Arg Ala Trp Ile Trp Asn Lys Trp Lys Ser Ala Gly Ala Glu Thr Leu
65 70 75 80

GAA GTG CAT CCC TGC GAG CAA GAA GAC AGA TCC GCA GAA GGA CCT TAA 288
Glu Val His Pro Cys Glu Gln Glu Asp Arg Ser Ala Glu Gly Pro
85 90 95

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 95 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

Met Ile Pro Met Arg Glu Ser Pro Pro Thr Arg Pro Cys Ser Thr Pro
1 5 10 15

Thr Ser Lys Asn Arg Glu Thr Val Pro Lys Ala Arg Gly Gly Pro Ser
20 25 30

Gln Glu Thr Arg Thr Gly Leu Cys His Gly Thr Ala Gln Thr Lys Ala
35 40 45

Phe Gly Ser Gly Gln Thr Val Val Leu Leu Gln Pro His Ala Ala Val
50 55 60

Arg Ala Trp Ile Trp Asn Lys Trp Lys Ser Ala Gly Ala Glu Thr Leu
65 70 75 80

Glu Val His Pro Cys Glu Gln Glu Asp Arg Ser Ala Glu Gly Pro
85 90 95

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 222 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(vi) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..222

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

```
ATG GAA CTG CCC AAA CTA AAG CTT TCG GGA GTG GTC AGA CTG TCG TCT      48
Met Glu Leu Pro Lys Leu Lys Leu Ser Gly Val Val Arg Leu Ser Ser
 1               5                  10                  15

TAC TCC AGC CCC ACG CTG CAG TCC GTG CTT GGA TCT GGA ACA AAT GGA      96
Tyr Ser Ser Pro Thr Leu Gln Ser Val Leu Gly Ser Gly Thr Asn Gly
            20                  25                  30

AGA GTG CCG GTG CTG AGA CCC TTG AAG TGC ATC CCT GCG AGC AAG AAG     144
Arg Val Pro Val Leu Arg Pro Leu Lys Cys Ile Pro Ala Ser Lys Lys
        35                  40                  45

ACA GAT CCG CAG AAG GAC CTT AAG CCT GCC CCG CAG CAG TGT CGC CTG     192
Thr Asp Pro Gln Lys Asp Leu Lys Pro Ala Pro Gln Gln Cys Arg Leu
    50                  55                  60

CCC ACC ATA GTG CGG AAA GGC GGA AGA TAA                             222
```

Pro Thr Ile Val Arg Lys Gly Gly Arg
65 70

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 73 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

Met Glu Leu Pro Lys Leu Lys Leu Ser Gly Val Val Arg Leu Ser Ser
1 5 10 15

Tyr Ser Ser Pro Thr Leu Gln Ser Val Leu Gly Ser Gly Thr Asn Gly
20 25 30

Arg Val Pro Val Leu Arg Pro Leu Lys Cys Ile Pro Ala Ser Lys Lys
35 40 45

Thr Asp Pro Gln Lys Asp Leu Lys Pro Ala Pro Gln Gln Cys Arg Leu
50 55 60

Pro Thr Ile Val Arg Lys Gly Gly Arg
65 70

(2) INFORMATION FOR SEQ ID NO:12:

BNSDOCID: <WO 9629409A2 I >

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1168 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Homo sapiens

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

CTGTGACTGG TGCTGGAGTT TTGAGTCCAC AGATAAAATG TGTCTCCTTC GTCTCTACTA 60

GAGAGGAAAA AGAACTGGAA TTGGAAGAAC AGGGAGACTG AAGGGTAGCA AGAGAGGCTG 120

GAGAAGAGAG TGAAAAGACC GCTTACCTGA TTTGAAATTG TCTGCAGCCC CTCTTTCCTG 180

GAGTAAATGA ACTGGACCAA ATCTCAAAAA TCCACGATGT CATCGGCACA CCCGCTCAGA 240

AGATCCTCAC CAAGTTCAAA CAGTCGAGAG CTATGAATTT TGATTTTCCT TTTAAAAAGG 300

GATCAGGAAT ACCTCTACTA ACAACCAATT TGTCCCCACA ATGCCTCTCC CTCCTGCACG 360

BNSDOCID: <WO 9629409A2 1 >

CAATGGTGGC CTATGATCCC GATGAGAGAA TCGCCGCCCA CCAGGCCCTG CAGCACCCCT 420

ACTTCCAAGA ACAGAGAAAC AGTCCCTAAA GCAAGAGGAG GACCGTCCCA AGAGACGAGG 480

ACCGGCCTAT GTCATGGAAC TGCCCAAACT AAAGCTTTCG GGAGTGGTCA GACTGTCGTC 540

TTACTCCAGC CCCACGCTGC AGTCCGTGCT TGGATCTGGA ACAAATGGAA GAGTGCCGGT 600

GCTGAGACCC TTGAAGTGCA TCCCTGCGAG CAAGAAGACA GATCCGCAGA AGGACCTTAA 660

GCCTGCCCCG CAGCAGTGTC GCCTGCCCAC CATAGTGCGG AAAGGCGGAA GATAACTGAG 720

CAGCACCGTC GTCTCGACTT CGGAGGCAAC ACCAAGCCCG ACCGGGCCAG GCCTGGGTGA 780

TCTGCTGCTG AGACGCCACG GAGGGCTGGG GATGCGCCTG CGTCCGTTTC GCGCTGGCCG 840

GGGCTCTGGG TGCTGCCCTG CGCCCTGCCG CACCCGCGGC CCGCGCAGCT GCCTAGGATG 900

TTCTGGGCTA ATATACTTGT AAAACCACCG CATTCTAGGG TTTTCTTTCA TTTTCGTTAA 960

GAATTTGGGG CAGGAAATAC TTTGTAACTT TGTATATGAA TCAAAACAAA CGAGCAGGCA 1020

TTTCTGTGAT GTGTTGGGCG TGGTTGGAAG GTGGGTTCTG CGTGTCCCTT CCCAGCGCTG 1080

CTGGTCAGTC GTGGAGCGCC ATCATGTCTT ACCAGTGACG CTGCTGACAC CCCTGACTTT 1140

TATTAAAGAA TAAGCTGTCG TTAAAAAA 1168

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1235 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Homo sapiens

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

ATTCCTGAGT CTGTGACTGG TGCTGGAGTT TTGAGTCCAC AGATAAAATG TGTCTCCTTC 60

GTCTCTACTA GAGAGGAAAA AGAACTGGAA TTGGAAGAAC AGGGAGACTG AAGGGTAGCA 120

AGAGAGGCTG GAGAAGAGAG TGAAAAGACC GCTTACCTGA TTTGAAATTG ATGGTGGCGT 180

GGGAATGAAG AATGTGATAT ACATCTTTGG AGTCTGTTCT GCAGCCCCTC TTTCCTGGAG 240

TAAATGAACT GGACCAAATC TCAAAAATCC ACGATGTCAT CGGCACACCC GCTCAGAAGA 300

TCCTCACCAA GTTCAAACAG TCGAGAGCTA TGAATTTTGA TTTTCCTTTT AAAAAGGGAT 360

CAGGAATACC TCTACTAACA ACCAATTTGT CCCCACAATG CCTCTCCCTC CTGCACGCAA 420

TGGTGGCCTA TGATCCCGAT GAGAGAATCG CCGCCCACCA GGCCCTGCAG CACCCCTACT 480

TCCAAGAACA GAGAAACAGT CCCTAAAGCA AGAGGAGGAC CGTCCCAAGA GACGAGGACC 540

GGCCTATGTC ATGGAACTGC CCAAACTAAA GCTTTCGGGA GTGGTCAGAC TGTCGTCTTA 600

CTCCAGCCCC ACGCTGCAGT CCGTGCTTGG ATCTGGAACA AATGGAAGAG TGCCGGTGCT 660

GAGACCCTTG AAGTGCATCC CTGCGAGCAA GAAGACAGAT CCGCAGAAGG ACCTTAAGCC 720

TGCCCCGCAG CAGTGTCGCC TGCCCACCAT AGTGCGGAAA GGCGGAAGAT AACTGAGCAG 780

CACCGTCGTC TCGACTTCGG AGGCAACACC AAGCCCGACC GGGCCAGGCC TGGGTGATCT 840

GCTGCTGAGA CGCCACGGAG GGCTGGGGAT GCGCCTGCGT CCGTTTCGCG CTGGCCGGGG 900

CTCTGGGTGC TGCCCTGCGC CCTGCCGCAC CCGCGGCCCG CGCAGCTGCC TAGGATGTTC 960

TGGGCTAATA TACTTGTAAA ACCACCGCAT TCTAGGGTTT TCTTTCATTT TCGTTAAGAA 1020

TTTGGGGCAG GAAATACTTT GTAACTTTGT ATATGAATCA AAACAAACGA GCAGGCATTT 1080

CTGTGATGTG TTGGGCGTGG TTGGAAGGTG GGTTCTGCGT GTCCCTTCCC AGCGCTGCTG 1140

GTCAGTCGTG GAGCGCCATC ATGTCTTACC AGTGACGCTG CTGACACCCC TGACTTTTAT 1200

TAAAGAATAA GCTGTCGTTA CAGTATTGCA AAAAA 1235

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:

BNSDOCID: <WO 9629409A2 I >

(A) LENGTH: 2051 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Homo sapiens

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

GACTGGTGCT GGAGTTTTGA GTCCACAGAT AAAATGTGTC TCCTTCGTCT CTACTAGAGA 60

GGAAAAAGAA CTGGAATTGG AAGAACAGGG AGACTGAAGG GTAGCAAGAG AGGCTGGAGA 120

AGAGAGTGAA AAGACCGCTT ACCTGATTTG AAATTGTCTG CAGCCCCTCT TTCCTGGAGT 180

AAATGAACTG GACCAAATCT CAAAAATCCA CGATGTCATC GGCACACCCG CTCAGAAGAT 240

CCTCACCAAG TTCAAACAGT CGAGAGCTAT GAATTTTGAT TTTCCTTTTA AAAAGGGATC 300

AGGAATACCT CTACTAACAA CCAATTTGTC CCCACAATGC CTCTCCCTCC TGCACGCAAT 360

GGTGGCCTAT GATCCCGATG AGAGAATCGC CGCCCACCAG GCCCTGCAGC ACCCCTACTT 420

CCAAGAACAG AGAACCCAGA ACGGAAGCGA GGATGAAGGC CTCAGCCGTC CTCCTCCCCA 480

TTCAAACACG TTCATCCCTC AACCCTCTGC TGAGCACCTG CATGCTGCCC GGCCGCAGTG 540

TCACCCTTCT TGTGTGAGCC TACCCTCATC CACCCACCTC ACCCTCCTGA CCTTAAAGAA 600

GACACCGGGC AGAAGCACAG GGGAGCCCAG TCACACCCCA CACTGGCGGG GGCAGGCCTT 660

GCAGGGAGAA GCAGTAAGCA GCCATCTCCA TCAGCCATTT CCATCTGGCA CTCAGACGTG 720

CACGTCTTCG TGTGACAGGC GGCAGCAGTG CGACCGTGAC CTCCCATCTG CTCTGCTGTC 780

CCCACACCTG CGGTGCAGCC AGCCTGCCAC AAGGCAGCTA GAGTCCAGCT AGACCCACCC 840

CTGGCACGGC CGACCTCTTC CTGGCTTCTT CTGGGCCTAA TCCCCGTGCA TTCTCCAACG 900

CCAGAAGTGT AAGAAAGTGC AAGGCAACAA GTGAGAAGAG CAAACCCAAA TCGTACCAGG 960

GAAGCTAGTC TTTCCAGGGC ACCTGAGTGA GGGCATGACC AGCCTTGACG CTGCCTCGCT 1020

ACCATCTGCC CAGGGCCTGC TGAATGCTTG AGTCCATGGT GACAGTGGTG GGAACAGTTA 1080

CGAGGCAGTT AGATTTTGGA AGTCATGTTG GCCCACTTGG CTACAGAGCA GTCTTAGGAA 1140

CAGCACCATA AAAATAAAGA CTTATTCCTG ACACACATGC ATCTAGAGTA AACTGGGGCG 1200

TATCTGACAG CGTTAGTACA GTGATGGCCA AATGCAAACT GCATTCCAGA ACCAGCGAAG 1260

GGTGACAGAC TGGGCTGAGG CAGAGCTAGG ACTAACCATC TCGAGTGATG CCATCTCGGG 1320

GCCAACAAAA GTTTTGGACA CGGCTGGATC ATCTGACCAA ACTGCTCAAA TCTTTACACA 1380

ATTATTGTCC TGGTATTAAA CTTTCACCTG CCACTTCCAA CAAACAGGAG ACAGAATAAG 1440

GAGATGACCA GGAAGATGGC TGGATTAAGA ATTCTAGACT TGGCCGGGTG CGGTGGCTCA 1500

CACCTGTAAT CCTAGCATCT TGGGAGGCTG AGGCAGGAGG ATCGCTTGAG CCCAGAGTTT 1560

GAGACCAGCC TAGGCAACAT AAGGAGACCC CATCTCTACA AAATATCAAA AAATTACCCA 1620

GGTATGGTGG CACACACGTG TGATTCCAGC TACTCGGGAG GCTGAGATGG GAGGATCACT 1680

TGAACCCAGG AGGTTGGGGC TACAATGAGC TATGATCGCA CCACTTCATT CCAGCCTGGA 1740

TGACAGAAGA CTCACTCCAT AGTTCATGGC CCCGTGATCC AGAGTCCCTG CTGGCGCCTT 1800

CGAGTGGGGC AGGCTGAGAA CTCAAGCTGT AACTAATGTC TCCTCCGAAG AAAACTAAAC 1860

CGAGGGCTGA GCTGATGTGA AGTTTTCCGT GGCTGCATTC ATACAAATGG TGAAAATGTA 1920

GCATACCTCC CCTCAAAAGC CTGAAAGTAA AGACATGCCC CCAATTTAAT GTGATGAATT 1980

AGAGAAATAG GTTTCAGACA CTTCATGGTT TAAAGTCTCA CAAAATAAAG CTTTCGAAGG 2040

AAAAAAAAAA A 2051

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 60 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Homo sapiens

(ix) FEATURE:

(A) NAME/KEY: CDS

(B) LOCATION: 1..60

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

```
ATG TCA TCG GCA CAC CCG CTC AGA AGA TCC TCA CCA AGT TCA AAC AGT        48
Met Ser Ser Ala His Pro Leu Arg Arg Ser Ser Pro Ser Ser Asn Ser
 1               5                  10                  15

CGA GAG CTA TGA                                                     60
Arg Glu Leu
```

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 19 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

Met Ser Ser Ala His Pro Leu Arg Arg Ser Ser Pro Ser Ser Asn Ser
1 5 10 15

Arg Glu Leu

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 177 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(vi) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(ix) FEATURE:

(A) NAME/KEY: CDS

(B) LOCATION: 1..177

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

```
ATG AAT TTT GAT TTT CCT TTT AAA AAG GGA TCA GGA ATA CCT CTA CTA      48
Met Asn Phe Asp Phe Pro Phe Lys Lys Gly Ser Gly Ile Pro Leu Leu
 1               5                  10                  15

ACA ACC AAT TTG TCC CCA CAA TGC CTC TCC CTC CTG CAC GCA ATG GTG      96
Thr Thr Asn Leu Ser Pro Gln Cys Leu Ser Leu Leu His Ala Met Val
            20                  25                  30

GCC TAT GAT CCC GAT GAG AGA ATC GCC GCC CAC CAG GCC CTG CAG CAC     144
Ala Tyr Asp Pro Asp Glu Arg Ile Ala Ala His Gln Ala Leu Gln His
        35                  40                  45

CCC TAC TTC CAA GAA CAG AGA AAC AGT CCC TAA                         177
Pro Tyr Phe Gln Glu Gln Arg Asn Ser Pro
    50                  55
```

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 58 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

BNSDOCID: <WO ..9629409A2 1 >

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

Met Asn Phe Asp Phe Pro Phe Lys Lys Gly Ser Gly Ile Pro Leu Leu
1 5 10 15

Thr Thr Asn Leu Ser Pro Gln Cys Leu Ser Leu Leu His Ala Met Val
20 25 30

Ala Tyr Asp Pro Asp Glu Arg Ile Ala Ala His Gln Ala Leu Gln His
35 40 45

Pro Tyr Phe Gln Glu Gln Arg Asn Ser Pro
50 55

(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 288 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(vi) ORIGINAL SOURCE:

BNSDOCID: <WO 9629409A2 I >

(A) ORGANISM: Homo sapiens

(ix) FEATURE:

(A) NAME/KEY: CDS

(B) LOCATION: 1..288

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

```
ATG ATC CCG ATG AGA GAA TCG CCG CCC ACC AGG CCC TGC AGC ACC CCT      48
Met Ile Pro Met Arg Glu Ser Pro Pro Thr Arg Pro Cys Ser Thr Pro
 1               5                  10                  15

ACT TCC AAG AAC AGA GAA ACA GTC CCT AAA GCA AGA GGA GGA CCG TCC      96
Thr Ser Lys Asn Arg Glu Thr Val Pro Lys Ala Arg Gly Gly Pro Ser
            20                  25                  30

CAA GAG ACG AGG ACC GGC CTA TGT CAT GGA ACT GCC CAA ACT AAA GCT     144
Gln Glu Thr Arg Thr Gly Leu Cys His Gly Thr Ala Gln Thr Lys Ala
        35                  40                  45

TTC GGG AGT GGT CAG ACT GTC GTC TTA CTC CAG CCC CAC GCT GCA GTC     192
Phe Gly Ser Gly Gln Thr Val Val Leu Leu Gln Pro His Ala Ala Val
    50                  55                  60

CGT GCT TGG ATC TGG AAC AAA TGG AAG AGT GCC GGT GCT GAG ACC CTT     240
Arg Ala Trp Ile Trp Asn Lys Trp Lys Ser Ala Gly Ala Glu Thr Leu
65                  70                  75                  80

GAA GTG CAT CCC TGC GAG CAA GAA GAC AGA TCC GCA GAA GGA CCT TAA     288
Glu Val His Pro Cys Glu Gln Glu Asp Arg Ser Ala Glu Gly Pro
                85                  90                  95
```

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 95 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

Met Ile Pro Met Arg Glu Ser Pro Pro Thr Arg Pro Cys Ser Thr Pro
1 5 10 15

Thr Ser Lys Asn Arg Glu Thr Val Pro Lys Ala Arg Gly Gly Pro Ser
20 25 30

Gln Glu Thr Arg Thr Gly Leu Cys His Gly Thr Ala Gln Thr Lys Ala
35 40 45

Phe Gly Ser Gly Gln Thr Val Val Leu Leu Gln Pro His Ala Ala Val
50 55 60

Arg Ala Trp Ile Trp Asn Lys Trp Lys Ser Ala Gly Ala Glu Thr Leu
65 70 75 80

Glu Val His Pro Cys Glu Gln Glu Asp Arg Ser Ala Glu Gly Pro
85 90 95

(2) INFORMATION FOR SEQ ID NO:21:

BNSDOCID <WO 9629409A2 >

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 222 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Homo sapiens

(ix) FEATURE:

(A) NAME/KEY: CDS

(B) LOCATION: 1..222

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

```
ATG GAA CTG CCC AAA CTA AAG CTT TCG GGA GTG GTC AGA CTG TCG TCT      48
Met Glu Leu Pro Lys Leu Lys Leu Ser Gly Val Val Arg Leu Ser Ser
 1               5                  10                  15

TAC TCC AGC CCC ACG CTG CAG TCC GTG CTT GGA TCT GGA ACA AAT GGA      96
Tyr Ser Ser Pro Thr Leu Gln Ser Val Leu Gly Ser Gly Thr Asn Gly
            20                  25                  30
```

AGA GTG CCG GTG CTG AGA CCC TTG AAG TGC ATC CCT GCG AGC AAG AAG 144
Arg Val Pro Val Leu Arg Pro Leu Lys Cys Ile Pro Ala Ser Lys Lys
35 40 45

ACA GAT CCG CAG AAG GAC CTT AAG CCT GCC CCG CAG CAG TGT CGC CTG 192
Thr Asp Pro Gln Lys Asp Leu Lys Pro Ala Pro Gln Gln Cys Arg Leu
50 55 60

CCC ACC ATA GTG CGG AAA GGC GGA AGA TAA 222
Pro Thr Ile Val Arg Lys Gly Gly Arg
65 70

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 73 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

Met Glu Leu Pro Lys Leu Lys Leu Ser Gly Val Val Arg Leu Ser Ser
1 5 10 15

Tyr Ser Ser Pro Thr Leu Gln Ser Val Leu Gly Ser Gly Thr Asn Gly
20 25 30

Arg Val Pro Val Leu Arg Pro Leu Lys Cys Ile Pro Ala Ser Lys Lys
35 40 45

RNSDOCID <WO 9629409A2 I >

Thr Asp Pro Gln Lys Asp Leu Lys Pro Ala Pro Gln Gln Cys Arg Leu
50 55 60

Pro Thr Ile Val Arg Lys Gly Gly Arg
65 70

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 63 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(vi) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..63

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

BNSDOCID: <WO 9629409A2 I >

ATG AAG AAT GTG ATA TAC ATC TTT GGA GTC TGT TCT GCA GCC CCT CTT 48
Met Lys Asn Val Ile Tyr Ile Phe Gly Val Cys Ser Ala Ala Pro Leu
1 5 10 15

TCC TGG AGT AAA TGA 63
Ser Trp Ser Lys
20

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

Met Lys Asn Val Ile Tyr Ile Phe Gly Val Cys Ser Ala Ala Pro Leu
1 5 10 15

Ser Trp Ser Lys
20

(2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 60 base pairs
(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Homo sapiens

(ix) FEATURE:

(A) NAME/KEY: CDS

(B) LOCATION: 1..60

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

```
ATG TCA TCG GCA CAC CCG CTC AGA AGA TCC TCA CCA AGT TCA AAC AGT        48
Met Ser Ser Ala His Pro Leu Arg Arg Ser Ser Pro Ser Ser Asn Ser
 1               5                  10                  15

CGA GAG CTA TGA                                                     60
Arg Glu Leu
```

(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 19 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

Met Ser Ser Ala His Pro Leu Arg Arg Ser Ser Pro Ser Ser Asn Ser
1 5 10 15

Arg Glu Leu

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 177 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Homo sapiens

(ix) FEATURE:

(A) NAME/KEY: CDS

(B) LOCATION: 1..177

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

```
ATG AAT TTT GAT TTT CCT TTT AAA AAG GGA TCA GGA ATA CCT CTA CTA      48
Met Asn Phe Asp Phe Pro Phe Lys Lys Gly Ser Gly Ile Pro Leu Leu
 1               5                  10                  15

ACA ACC AAT TTG TCC CCA CAA TGC CTC TCC CTC CTG CAC GCA ATG GTG      96
Thr Thr Asn Leu Ser Pro Gln Cys Leu Ser Leu Leu His Ala Met Val
            20                  25                  30

GCC TAT GAT CCC GAT GAG AGA ATC GCC GCC CAC CAG GCC CTG CAG CAC     144
Ala Tyr Asp Pro Asp Glu Arg Ile Ala Ala His Gln Ala Leu Gln His
        35                  40                  45

CCC TAC TTC CAA GAA CAG AGA AAC AGT CCC TAA                         177
Pro Tyr Phe Gln Glu Gln Arg Asn Ser Pro
    50                  55
```

(2) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 58 amino acids

(B) TYPE: amino acid

BNSDOCID: <WO__9629409A2_I_>

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

Met Asn Phe Asp Phe Pro Phe Lys Lys Gly Ser Gly Ile Pro Leu Leu
1 5 10 15

Thr Thr Asn Leu Ser Pro Gln Cys Leu Ser Leu Leu His Ala Met Val
20 25 30

Ala Tyr Asp Pro Asp Glu Arg Ile Ala Ala His Gln Ala Leu Gln His
35 40 45

Pro Tyr Phe Gln Glu Gln Arg Asn Ser Pro
50 55

(2) INFORMATION FOR SEQ ID NO:29:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 288 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Homo sapiens

(ix) FEATURE:

(A) NAME/KEY: CDS

(B) LOCATION: 1..288

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

```
ATG ATC CCG ATG AGA GAA TCG CCG CCC ACC AGG CCC TGC AGC ACC CCT      48
Met Ile Pro Met Arg Glu Ser Pro Pro Thr Arg Pro Cys Ser Thr Pro
 1               5                  10                  15

ACT TCC AAG AAC AGA GAA ACA GTC CCT AAA GCA AGA GGA GGA CCG TCC      96
Thr Ser Lys Asn Arg Glu Thr Val Pro Lys Ala Arg Gly Gly Pro Ser
            20                  25                  30

CAA GAG ACG AGG ACC GGC CTA TGT CAT GGA ACT GCC CAA ACT AAA GCT     144
Gln Glu Thr Arg Thr Gly Leu Cys His Gly Thr Ala Gln Thr Lys Ala
        35                  40                  45

TTC GGG AGT GGT CAG ACT GTC GTC TTA CTC CAG CCC CAC GCT GCA GTC     192
Phe Gly Ser Gly Gln Thr Val Val Leu Leu Gln Pro His Ala Ala Val
    50                  55                  60

CGT GCT TGG ATC TGG AAC AAA TGG AAG AGT GCC GGT GCT GAG ACC CTT     240
Arg Ala Trp Ile Trp Asn Lys Trp Lys Ser Ala Gly Ala Glu Thr Leu
65                  70                  75                  80
```

BNSDOCID: <WO___9629409A2_I_>

GAA GTG CAT CCC TGC GAG CAA GAA GAC AGA TCC GCA GAA GGA CCT TAA 288
Glu Val His Pro Cys Glu Gln Glu Asp Arg Ser Ala Glu Gly Pro
85 90 95

(2) INFORMATION FOR SEQ ID NO:30:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 95 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

Met Ile Pro Met Arg Glu Ser Pro Pro Thr Arg Pro Cys Ser Thr Pro
1 5 10 15

Thr Ser Lys Asn Arg Glu Thr Val Pro Lys Ala Arg Gly Gly Pro Ser
20 25 30

Gln Glu Thr Arg Thr Gly Leu Cys His Gly Thr Ala Gln Thr Lys Ala
35 40 45

Phe Gly Ser Gly Gln Thr Val Val Leu Leu Gln Pro His Ala Ala Val
50 55 60

Arg Ala Trp Ile Trp Asn Lys Trp Lys Ser Ala Gly Ala Glu Thr Leu
65 70 75 80

BNSDOCID: <WO 9629409A2 I >

Glu Val His Pro Cys Glu Gln Glu Asp Arg Ser Ala Glu Gly Pro
85 90 95

(2) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 222 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(vi) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..222

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

```
ATG GAA CTG CCC AAA CTA AAG CTT TCG GGA GTG GTC AGA CTG TCG TCT        48
Met Glu Leu Pro Lys Leu Lys Leu Ser Gly Val Val Arg Leu Ser Ser
 1               5                  10                  15

TAC TCC AGC CCC ACG CTG CAG TCC GTG CTT GGA TCT GGA ACA AAT GGA        96
Tyr Ser Ser Pro Thr Leu Gln Ser Val Leu Gly Ser Gly Thr Asn Gly
            20                  25                  30

AGA GTG CCG GTG CTG AGA CCC TTG AAG TGC ATC CCT GCG AGC AAG AAG       144
Arg Val Pro Val Leu Arg Pro Leu Lys Cys Ile Pro Ala Ser Lys Lys
        35                  40                  45

ACA GAT CCG CAG AAG GAC CTT AAG CCT GCC CCG CAG CAG TGT CGC CTG       192
Thr Asp Pro Gln Lys Asp Leu Lys Pro Ala Pro Gln Gln Cys Arg Leu
    50                  55                  60

CCC ACC ATA GTG CGG AAA GGC GGA AGA TAA                               222
Pro Thr Ile Val Arg Lys Gly Gly Arg
65                  70
```

(2) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 73 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

BNSDOCID: <WO 9629409A2 I >

Met Glu Leu Pro Lys Leu Lys Leu Ser Gly Val Val Arg Leu Ser Ser
1 5 10 15

Tyr Ser Ser Pro Thr Leu Gln Ser Val Leu Gly Ser Gly Thr Asn Gly
20 25 30

Arg Val Pro Val Leu Arg Pro Leu Lys Cys Ile Pro Ala Ser Lys Lys
35 40 45

Thr Asp Pro Gln Lys Asp Leu Lys Pro Ala Pro Gln Gln Cys Arg Leu
50 55 60

Pro Thr Ile Val Arg Lys Gly Gly Arg
65 70

(2) INFORMATION FOR SEQ ID NO:33:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 60 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

BNSDOCID: <WO 9629409A2 I >

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Homo sapiens

(ix) FEATURE:

(A) NAME/KEY: CDS

(B) LOCATION: 1..60

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

```
ATG TCA TCG GCA CAC CCG CTC AGA AGA TCC TCA CCA AGT TCA AAC AGT        48
Met Ser Ser Ala His Pro Leu Arg Arg Ser Ser Pro Ser Ser Asn Ser
 1               5                  10                  15

CGA GAG CTA TGA                                                     60
Arg Glu Leu
```

(2) INFORMATION FOR SEQ ID NO:34:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 19 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

Met Ser Ser Ala His Pro Leu Arg Arg Ser Ser Pro Ser Ser Asn Ser
1 5 10 15

Arg Glu Leu

(2) INFORMATION FOR SEQ ID NO:35:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 564 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(vi) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..564

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:

```
ATG AAT TTT GAT TTT CCT TTT AAA AAG GGA TCA GGA ATA CCT CTA CTA      48
Met Asn Phe Asp Phe Pro Phe Lys Lys Gly Ser Gly Ile Pro Leu Leu
 1               5                  10                  15

ACA ACC AAT TTG TCC CCA CAA TGC CTC TCC CTC CTG CAC GCA ATG GTG      96
Thr Thr Asn Leu Ser Pro Gln Cys Leu Ser Leu Leu His Ala Met Val
            20                  25                  30

GCC TAT GAT CCC GAT GAG AGA ATC GCC GCC CAC CAG GCC CTG CAG CAC     144
Ala Tyr Asp Pro Asp Glu Arg Ile Ala Ala His Gln Ala Leu Gln His
        35                  40                  45

CCC TAC TTC CAA GAA CAG AGA ACC CAG AAC GGA AGC GAG GAT GAA GGC     192
Pro Tyr Phe Gln Glu Gln Arg Thr Gln Asn Gly Ser Glu Asp Glu Gly
    50                  55                  60

CTC AGC CGT CCT CCT CCC CAT TCA AAC ACG TTC ATC CCT CAA CCC TCT     240
Leu Ser Arg Pro Pro Pro His Ser Asn Thr Phe Ile Pro Gln Pro Ser
65                  70                  75                  80

GCT GAG CAC CTG CAT GCT GCC CGG CCG CAG TGT CAC CCT TCT TGT GTG     288
Ala Glu His Leu His Ala Ala Arg Pro Gln Cys His Pro Ser Cys Val
                85                  90                  95

AGC CTA CCC TCA TCC ACC CAC CTC ACC CTC CTG ACC TTA AAG AAG ACA     336
Ser Leu Pro Ser Ser Thr His Leu Thr Leu Leu Thr Leu Lys Lys Thr
            100                 105                 110

CCG GGC AGA AGC ACA GGG GAG CCC AGT CAC ACC CCA CAC TGG CGG GGG     384
Pro Gly Arg Ser Thr Gly Glu Pro Ser His Thr Pro His Trp Arg Gly
        115                 120                 125
```

CAG GCC TTG CAG GGA GAA GCA GTA AGC AGC CAT CTC CAT CAG CCA TTT 432
Gln Ala Leu Gln Gly Glu Ala Val Ser Ser His Leu His Gln Pro Phe
130 135 140

CCA TCT GGC ACT CAG ACG TGC ACG TCT TCG TGT GAC AGG CGG CAG CAG 480
Pro Ser Gly Thr Gln Thr Cys Thr Ser Ser Cys Asp Arg Arg Gln Gln
145 150 155 160

TGC GAC CGT GAC CTC CCA TCT GCT CTG CTG TCC CCA CAC CTG CGG TGC 528
Cys Asp Arg Asp Leu Pro Ser Ala Leu Leu Ser Pro His Leu Arg Cys
165 170 175

AGC CAG CCT GCC ACA AGG CAG CTA GAG TCC AGC TAG 564
Ser Gln Pro Ala Thr Arg Gln Leu Glu Ser Ser
180 185

(2) INFORMATION FOR SEQ ID NO:36:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 187 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:

Met Asn Phe Asp Phe Pro Phe Lys Lys Gly Ser Gly Ile Pro Leu Leu
1 5 10 15

Thr Thr Asn Leu Ser Pro Gln Cys Leu Ser Leu Leu His Ala Met Val
20 25 30

Ala Tyr Asp Pro Asp Glu Arg Ile Ala Ala His Gln Ala Leu Gln His
35 40 45

Pro Tyr Phe Gln Glu Gln Arg Thr Gln Asn Gly Ser Glu Asp Glu Gly
50 55 60

Leu Ser Arg Pro Pro Pro His Ser Asn Thr Phe Ile Pro Gln Pro Ser
65 70 75 80

Ala Glu His Leu His Ala Ala Arg Pro Gln Cys His Pro Ser Cys Val
85 90 95

Ser Leu Pro Ser Ser Thr His Leu Thr Leu Leu Thr Leu Lys Lys Thr
100 105 110

Pro Gly Arg Ser Thr Gly Glu Pro Ser His Thr Pro His Trp Arg Gly
115 120 125

Gln Ala Leu Gln Gly Glu Ala Val Ser Ser His Leu His Gln Pro Phe
130 135 140

Pro Ser Gly Thr Gln Thr Cys Thr Ser Ser Cys Asp Arg Arg Gln Gln
145 150 155 160

Cys Asp Arg Asp Leu Pro Ser Ala Leu Leu Ser Pro His Leu Arg Cys
165 170 175

Ser Gln Pro Ala Thr Arg Gln Leu Glu Ser Ser
180 185

(2) INFORMATION FOR SEQ ID NO:37:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 189 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Homo sapiens

(ix) FEATURE:

(A) NAME/KEY: CDS

(B) LOCATION: 1..189

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:

```
ATG ATC CCG ATG AGA GAA TCG CCG CCC ACC AGG CCC TGC AGC ACC CCT      48
Met Ile Pro Met Arg Glu Ser Pro Pro Thr Arg Pro Cys Ser Thr Pro
 1               5                  10                  15
```

ACT TCC AAG AAC AGA GAA CCC AGA ACG GAA GCG AGG ATG AAG GCC TCA 96
Thr Ser Lys Asn Arg Glu Pro Arg Thr Glu Ala Arg Met Lys Ala Ser
20 25 30

GCC GTC CTC CTC CCC ATT CAA ACA CGT TCA TCC CTC AAC CCT CTG CTG 144
Ala Val Leu Leu Pro Ile Gln Thr Arg Ser Ser Leu Asn Pro Leu Leu
35 40 45

AGC ACC TGC ATG CTG CCC GGC CGC AGT GTC ACC CTT CTT GTG TGA 189
Ser Thr Cys Met Leu Pro Gly Arg Ser Val Thr Leu Leu Val
50 55 60

(2) INFORMATION FOR SEQ ID NO:38:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 62 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(iii) HYPOTHETICAL: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:

Met Ile Pro Met Arg Glu Ser Pro Pro Thr Arg Pro Cys Ser Thr Pro
1 5 10 15

Thr Ser Lys Asn Arg Glu Pro Arg Thr Glu Ala Arg Met Lys Ala Ser
20 25 30

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Ala Val Leu Leu Pro Ile Gln Thr Arg Ser Ser Leu Asn Pro Leu Leu
35 40 45

Ser Thr Cys Met Leu Pro Gly Arg Ser Val Thr Leu Leu Val
50 55 60

(2) INFORMATION FOR SEQ ID NO:39:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(v) FRAGMENT TYPE: internal

(vi) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:39:

Ser Pro Ser Ser Asn Arg Ile Arg Asn Thr Ser Thr
1 5 10

(2) INFORMATION FOR SEQ ID NO:40:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 9 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(v) FRAGMENT TYPE: internal

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Homo sapiens

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:40:

Ser Pro Ser Ser Asn Arg Ile Arg Asn
1 5

(2) INFORMATION FOR SEQ ID NO:41:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 9 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

BNSDOCID: <WO 9629409A2 >

(v) FRAGMENT TYPE: internal

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Homo sapiens

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:41:

Pro Ser Ser Asn Arg Ile Arg Asn Thr
1 5

(2) INFORMATION FOR SEQ ID NO:42:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 9 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(v) FRAGMENT TYPE: internal

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Homo sapiens

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:42:

Ser Ser Asn Arg Ile Arg Asn Thr Ser
1 5

(2) INFORMATION FOR SEQ ID NO:43:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(v) FRAGMENT TYPE: internal

(vi) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:43:

Ser Pro Ser Ser Asn Arg Ile Arg Asn Thr
1 5 10

(2) INFORMATION FOR SEQ ID NO:44:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 27 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Homo sapiens

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:44:

TCACCAAGTT CAAACAGGAT CAGGAAT 27

(2) INFORMATION FOR SEQ ID NO:45:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 30 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Homo sapiens

BNSDOCID: <WO_ 9629409A2 I >

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:45:

TCACCAAGTT CAAACAGGAT CAGGAATACC 30

(2) INFORMATION FOR SEQ ID NO:46:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Homo sapiens

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:46:

GTGTCTCCTT CGTCTCTACT A 21

(2) INFORMATION FOR SEQ ID NO:47:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 18 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: YES

(v) FRAGMENT TYPE: internal

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Homo sapiens

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:47:

GGTGTGCCGA TGACATCG 18

(2) INFORMATION FOR SEQ ID NO:48:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 18 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: YES

(v) FRAGMENT TYPE: internal

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Homo sapiens

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:48:

GAGGTATTCC TGATCCTG 18

(2) INFORMATION FOR SEQ ID NO:49:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 13 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Homo sapiens

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:49:

CAAACANGGA TCA 13

(2) INFORMATION FOR SEQ ID NO:50:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(vi) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:50:

NTATTCCTGA TCCT 14

(2) INFORMATION FOR SEQ ID NO:51:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Homo sapiens

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:51:

NTATTCCTGA TCCTG 15

(2) INFORMATION FOR SEQ ID NO:52:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Homo sapiens

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:52:

NTATTCCTGA TCCTGT 16

(2) INFORMATION FOR SEQ ID NO:53:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 17 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Homo sapiens

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:53:

NTATTCCTGA TCCTGTT 17

(2) INFORMATION FOR SEQ ID NO:54:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 14 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: YES

(v) FRAGMENT TYPE: internal

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Homo sapiens

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:54:

NCAAGTTCAA ACAG 14

(2) INFORMATION FOR SEQ ID NO:55:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 15 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: YES

(v) FRAGMENT TYPE: internal

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Homo sapiens

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:55:

NCAAGTTCAA ACAGG 15

(2) INFORMATION FOR SEQ ID NO:56:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 9 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(v) FRAGMENT TYPE: internal

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Homo sapiens

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:40:

Ser Pro Ser Ser Asn Arg Ile Arg Asn
1 5

(2) INFORMATION FOR SEQ ID NO:41:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 9 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(v) FRAGMENT TYPE: internal

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Homo sapiens

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:41:

Pro Ser Ser Asn Arg Ile Arg Asn Thr
1 5

(2) INFORMATION FOR SEQ ID NO:42:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 9 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(v) FRAGMENT TYPE: internal

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Homo sapiens

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:42:

Ser Ser Asn Arg Ile Arg Asn Thr Ser
1 5

BNSDOCID: <WO 9629409A2 I >

(2) INFORMATION FOR SEQ ID NO:43:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 10 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(v) FRAGMENT TYPE: internal

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Homo sapiens

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:43:

Ser Pro Ser Ser Asn Arg Ile Arg Asn Thr
1 5 10

(2) INFORMATION FOR SEQ ID NO:44:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 27 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

BNSDOCID: <WO 9629409A2 I >

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(vi) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:44:

TCACCAAGTT CAAACAGGAT CAGGAAT 27

(2) INFORMATION FOR SEQ ID NO:45:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(vi) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

BNSDOCID: <WO_ 9629409A2 I >

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:45:

TCACCAAGTT CAAACAGGAT CAGGAATACC 30

(2) INFORMATION FOR SEQ ID NO:46:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Homo sapiens

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:46:

GTGTCTCCTT CGTCTCTACT A 21

(2) INFORMATION FOR SEQ ID NO:47:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 18 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: YES

(v) FRAGMENT TYPE: internal

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Homo sapiens

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:47:

GGTGTGCCGA TGACATCG 18

(2) INFORMATION FOR SEQ ID NO:48:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 18 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: YES

(v) FRAGMENT TYPE: internal

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Homo sapiens

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:48:

GAGGTATTCC TGATCCTG 18

(2) INFORMATION FOR SEQ ID NO:49:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 13 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Homo sapiens

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:49:

CAAACANGGA TCA 13

(2) INFORMATION FOR SEQ ID NO:50:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(vi) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:50:

NTATTCCTGA TCCT 14

(2) INFORMATION FOR SEQ ID NO:51:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Homo sapiens

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:51:

NTATTCCTGA TCCTG 15

(2) INFORMATION FOR SEQ ID NO:52:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Homo sapiens

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:52:

NTATTCCTGA TCCTGT 16

(2) INFORMATION FOR SEQ ID NO:53:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 17 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Homo sapiens

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:53:

NTATTCCTGA TCCTGTT 17

(2) INFORMATION FOR SEQ ID NO:54:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 14 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: YES

(v) FRAGMENT TYPE: internal

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Homo sapiens

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:54:

NCAAGTTCAA ACAG 14

(2) INFORMATION FOR SEQ ID NO:55:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 15 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: YES

(v) FRAGMENT TYPE: internal

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Homo sapiens

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:55:

NCAAGTTCAA ACAGG 15

(2) INFORMATION FOR SEQ ID NO:56:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

BNSDOCID: <WO 9629409A2 I >

(iv) ANTI-SENSE: YES

(v) FRAGMENT TYPE: internal

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Homo sapiens

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:56:

NCAAGTTCAA ACAGGA 16

(2) INFORMATION FOR SEQ ID NO:57:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 17 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: YES

(v) FRAGMENT TYPE: internal

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Homo sapiens

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:57:

NCAAGTTCAA ACAGGAT 17

BNSDOCID: <WO 9629409A2 I >

CLAIMS

1. An isolated polypeptide comprising the amino acid sequence of SEQ.ID.NO.40.

2. The isolated polypeptide of claim 1 wherein the isolated polypeptide comprises the amino acid sequence of SEQ.ID.NO.43.

3. The isolated polypeptide of claim 1 wherein the isolated polypeptide consists essentially of an amino acid sequence selected from the group consisting of SEQ.ID.NO.40 and SEQ.ID.NO.43.

4. The isolated polypeptide of claim 1 wherein the isolated polypeptide consists of an amino acid sequence selected from the group consisting of SEQ.ID.NO.40 and SEQ.ID.NO.43.

5. An isolated nucleic acid encoding a polypeptide selected from the group consisting of the polypeptide of claim 1, the polypeptide of claim 2. the polypeptide of claim 3 and the polypeptide of claim 4.

6. The isolated nucleic acid of claim 5 wherein the nucleic acid comprises SEQ.ID.NO.44.

7. An expression vector comprising the isolated nucleic acid of claim 5 operably linked to a promoter.

8. The expression vector of claim 7 wherein the nucleic acid comprises SEQ.ID.NO.44.

9. The expression vector of claims 7 or 8 further comprising a nucleic acid which codes for HLA-B7.

10. A host cell transfected or transformed with an expression vector selected from the group consisting of the expression vector of claim 7, the expression vector of claim 8 and the expression vector of claim 9.

11. A host cell transfected or transformed with an expression vector selected from the group of the expression vector of claim 7 and the expression vector of claim 8, and wherein the host cell expresses HLA-B7.

12. A kit for detecting the presence of the expression of a tumor rejection antigen precursor comprising:

a first primer selected from the group consisting of a nucleic acid consisting essentially of any one of SEQ.ID.NOs.50-57, and

a second primer constructed and arranged to selectively amplify together with the first primer a portion of ORF2 characteristic only of RAGE 1 genes.

13. A method for enriching selectively a population of T cells with cytolytic T cells specific for a RAGE tumor rejection antigen comprising:

contacting an isolated population of T cells with an agent presenting a complex of a RAGE tumor rejection antigen and HLA presenting molecule in an amount sufficient to selectively enrich said isolated population of T cells with said cytolytic T cells.

14. The method of claim 13 wherein the HLA presenting molecule is HLA-B7 and wherein the RAGE tumor rejection antigen is selected from the group consisting of:

a peptide consisting of the amino acids of SEQ.ID.NO.40 and a peptide consisting of the amino acids of SEQ.ID.NO.43.

15. A method for diagnosing a disorder characterized by expression of a RAGE tumor rejection antigen peptide, comprising:

contacting a biological sample isolated from a subject with an agent that is specific for the RAGE tumor rejection antigen peptide, and

determining the interaction between the agent and the RAGE tumor rejection antigen peptide as a determination of the disorder.

16. The method of claim 15 wherein the peptide is selected from the group consisting of:

a peptide consisting of the amino acids of SEQ.ID.NO.40 and a peptide consisting of the amino acids of SEQ.ID.NO.43.

17. A method for diagnosing a disorder characterized by expression of a RAGE tumor rejection antigen peptide which forms a complex with HLA-B7 molecules. comprising:

contacting a biological sample isolated from a subject with an agent that binds the complex; and

determining binding between the complex and the agent as a determination of the disorder.

18. The method of claim 17 wherein the peptide is selected from the group consisting of:

a peptide consisting of the amino acids of SEQ.ID.NO.40 and a peptide consisting of the amino acids of SEQ.ID.NO.43.

19. A method for treating a subject with a disorder characterized by expression of a RAGE tumor rejection antigen. comprising:

administering to the subject an amount of an agent which enriches selectively in the subject the presence of complexes of HLA-B7 and RAGE tumor rejection antigen. sufficient to ameliorate the disorder.

20. The method of claim 19 wherein the RAGE tumor rejection antigen is selected from the group consisting of:

a peptide consisting of the amino acids of SEQ.ID.NO.40 and a peptide consisting of the amino acids of SEQ.ID.NO.43.

21. A method for treating a subject with a disorder characterized by expression of a RAGE tumor rejection antigen, comprising:

administering to the subject an amount of autologous cytolytic T cells sufficient to ameliorate the disorder, the cytolytic T cells specific for complexes of an HLA-B7 molecule and a RAGE tumor rejection antigen.

22. The method of claim 21 wherein the RAGE tumor rejection antigen is selected from the group consisting of:

a peptide consisting of the amino acids of SEQ.ID.NO.40 and a peptide consisting of the amino acids of SEQ.ID.NO.43.

23. An isolated nucleic acid molecule which (a) hybridizes, under stringent conditions, to a molecule consisting of the nucleic acid sequence selected from the group consisting of: SEQ.ID.NO. 1; SEQ.ID.NO. 4; SEQ.ID.NO. 6; SEQ.ID.NO. 10; SEQ.ID.NO. 12; SEQ.ID.NO. 13; SEQ.ID.NO. 14; SEQ.ID.NO. 15; SEQ.ID.NO. 17; SEQ.ID.NO. 23; and/or SEQ.ID.NO. 35, and which codes for a tumor rejection antigen precursor, with the proviso that the isolated nucleic acid molecule does not code for a MAGE, GAGE, BAGE tumor rejection antigen precursor; and (b) nucleic acid molecules that differ from the nucleic acid molecules of (a) in codon sequence due to the degeneracy of the genetic code.

24. The isolated nucleic acid molecule of claim 23 wherein the isolated nucleic acid molecule is a cDNA molecule or an mRNA molecule.

25. The isolated nucleic acid molecule of claim 23 wherein the isolated nucleic acid molecule codes for a tumor rejection antigen precursor coded for by a molecule having a sequence selected from the group consisting of SEQ.ID.NO. 1, SEQ.ID.NO. 12; SEQ.ID.NO. 13; and/or SEQ.ID.NO. 14.

26. The isolated nucleic acid molecule of claim 23 wherein the isolated nucleic acid molecule comprises a nucleic acid molecule that is complementary to nucleotides selected from the group consisting of: 204 to 326 of SEQ.ID.NO. 1; 313 to 399 of

SEQ.ID.NO. 1; 444 to 665 of SEQ.ID.NO. 1; 273 to 449 of SEQ.ID.NO. 12; 217 to 276 of SEQ.ID.NO. 12; 185 to 247 of SEQ.ID.NO. 13; and/or 269 to 832 of SEQ.ID.NO. 14.

27. An isolated nucleic acid molecule consisting essentially of a nucleotide sequence selected from the group consisting of: SEQ.ID.NO. 1; SEQ.ID.NO. 4; SEQ.ID.NO. 6; SEQ.ID.NO. 10; SEQ.ID.NO. 12; SEQ.ID.NO. 13; SEQ.ID.NO. 14; SEQ.ID.NO. 15; SEQ.ID.NO. 17; SEQ.ID.NO. 23, SEQ.ID.NO. 35 and/or SEQ.ID.NO.45.

28. An expression vector comprising the isolated nucleic acid molecule of claims 23, 24, 25, 26 or 27, operably linked to a promoter.

29. A host cell transfected or transformed with the expression vector of claim 28.

30. An isolated nucleic acid consisting essentially of a unique fragment of a sequence selected from the group consisting of: SEQ.ID.NO. 1; SEQ.ID.NO. 12; SEQ.ID.NO. 13; SEQ.ID.NO. 14; the complement of SEQ.ID.NO. 1; the complement of SEQ.ID.NO. 12; the complement of SEQ.ID.NO. 13; and/or the complement of SEQ.ID.NO. 14.

31. The isolated nucleic acid of claim 30 wherein the fragment is between 200 and 2050 nucleotides in length.

32. The isolated nucleic acid of claim 30 wherein the fragment is 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31 and/or 32 nucleotides in length.

33. A kit for detecting the presence of the expression of the tumor rejection antigen precursor comprising a pair of isolated nucleic acid molecules constructed and arranged to selectively amplify the isolated nucleic acid molecule of claim 23.

BNSDOCID: <WO__9629409A2_I_>

34. The kit of claim 33 wherein the pair of isolated nucleic acid molecules are PCR primers.

35. An isolated tumor rejection antigen precursor coded for by the nucleic acid molecule of claims 23, 24, 25, 26 or 27.

36. A method for diagnosing a disorder characterized by expression of a RAGE tumor rejection antigen precursor which is processed to a RAGE derived tumor rejection antigen which forms a complex with HLA molecules, comprising:

contacting a biological sample isolated from a subject with an agent that binds said complex, and

determining binding between said complex and said agent as a determinant of said disorder.

37. A method for diagnosing a disorder characterized by expression of a RAGE tumor rejection antigen precursor coded for by a nucleic acid, comprising:

contacting a biological sample isolated from a subject with an agent that is specific for said nucleic acid or an expression product thereof, wherein the nucleic acid hybridizes under stringent conditions to a molecule consisting of the nucleic acid sequence selected from the group consisting of: SEQ.ID.NO.1; SEQ.ID.NO.4; SEQ.ID.NO.6; SEQ.ID.NO.10; SEQ.ID.NO. 12; SEQ.ID.NO. 13; SEQ.ID.NO. 14; SEQ.ID.NO. 15; SEQ.ID.NO. 17; SEQ.ID.NO. 23; and SEQ.ID.NO. 35, and which codes for a tumor rejection antigen precursor, with the proviso that the isolated nucleic acid molecule does not code for a MAGE, GAGE or BAGE tumor rejection antigen precursor. and

determining the interaction between said agent and said nucleic acid or said expression product as a determination of said disorder.

38. The method of claim 37 wherein the agent comprises a nucleic acid molecule selected from the group of molecules consisting of: SEQ.ID.NO. 1; SEQ.ID.NO. 12; SEQ.ID.NO. 13; SEQ.ID.NO. 14; a unique fragment of SEQ.ID.NO. 1;

a unique fragment of SEQ.ID.NO. 12; a unique fragment of SEQ.ID.NO. 13; and a unique fragment of SEQ.ID.NO. 14.

39. A method for treating a subject with a disorder characterized by expression of a RAGE tumor rejection antigen precursor, comprising

administering to said subject an amount of an agent, which enriches selectively in the subject the presence of complexes of HLA and tumor rejection antigen that is derived from a tumor rejection antigen precursor coded for by a molecule as described in claims 23, 24, 25, 26 or 27, sufficient to ameliorate said disorder.

40. A method for treating a subject with a disorder characterized by expression of a RAGE tumor rejection antigen precursor, comprising

administering to said subject an amount of autologous cytolytic T cells sufficient to ameliorate the disorder, the cytolytic T cells specific for complexes of an HLA molecule and a tumor rejection antigen that is derived from a tumor rejection antigen precursor coded for by a molecule as described in claims 23, 24, 25, 26 or 27 sufficient to ameliorate said disorder.

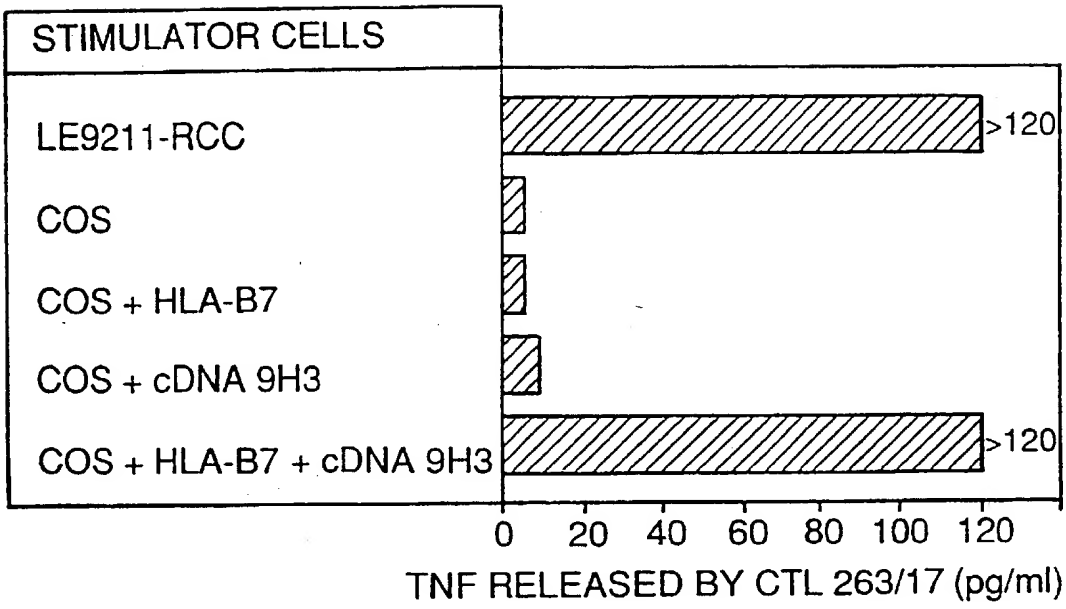

Fig. 1

BNSDOCID: <WO___9629409A2_I_>

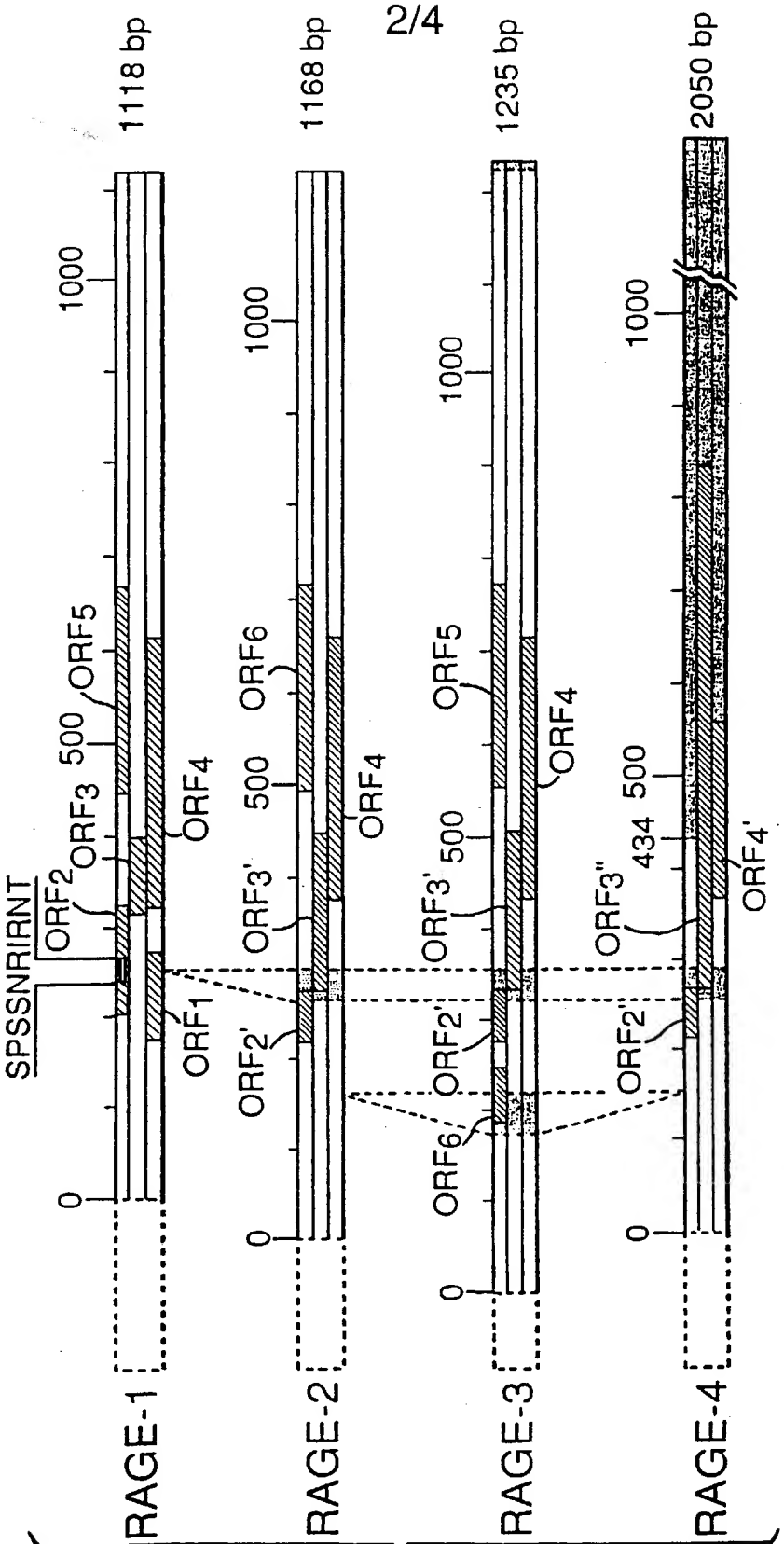

Fig. 2

BNSDOCID: <WO___9629409A2_I_>

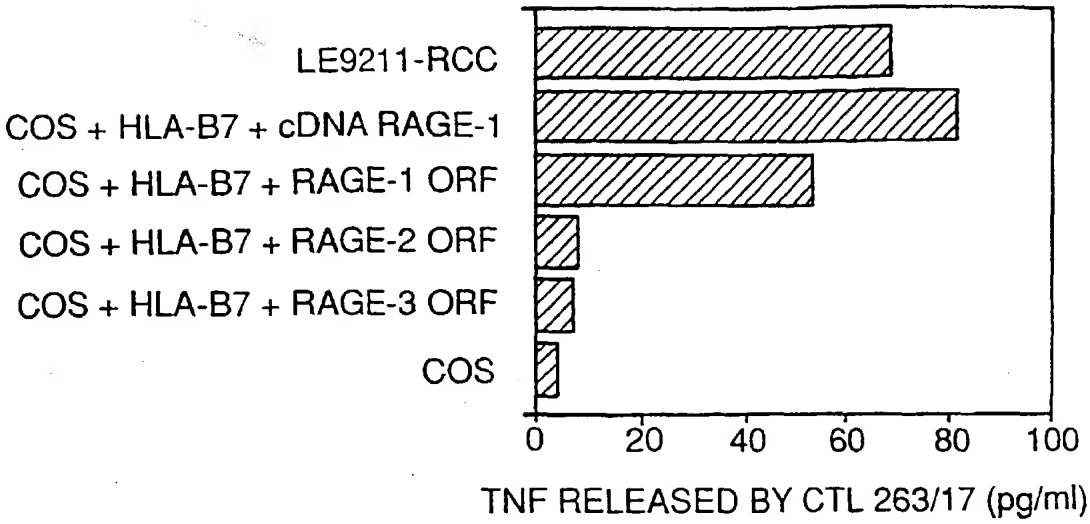

Fig. 3

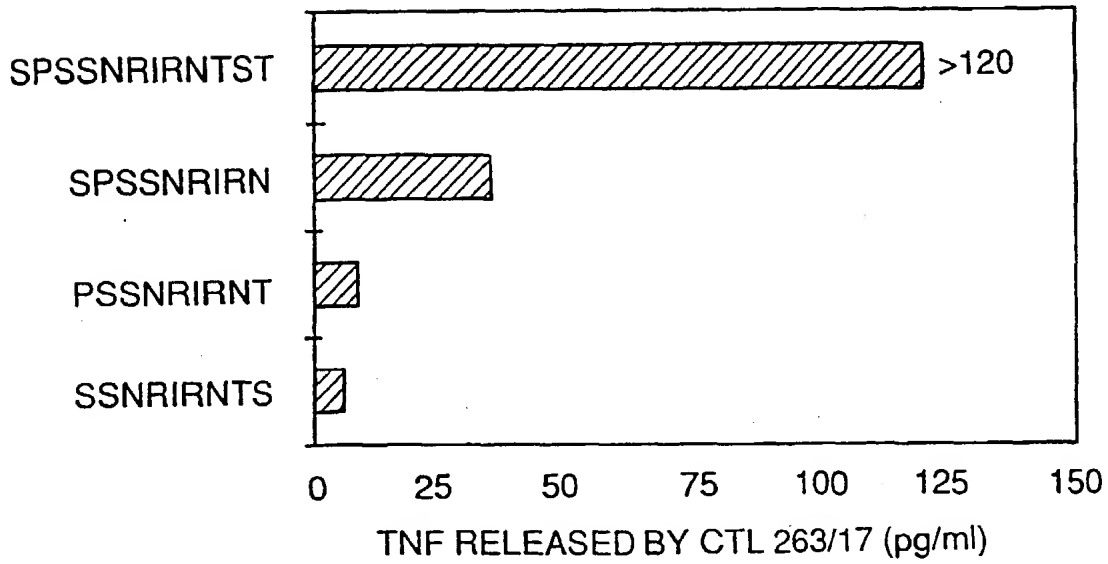

Fig. 4

BNSDOCID: <WO__9629409A2_I_>

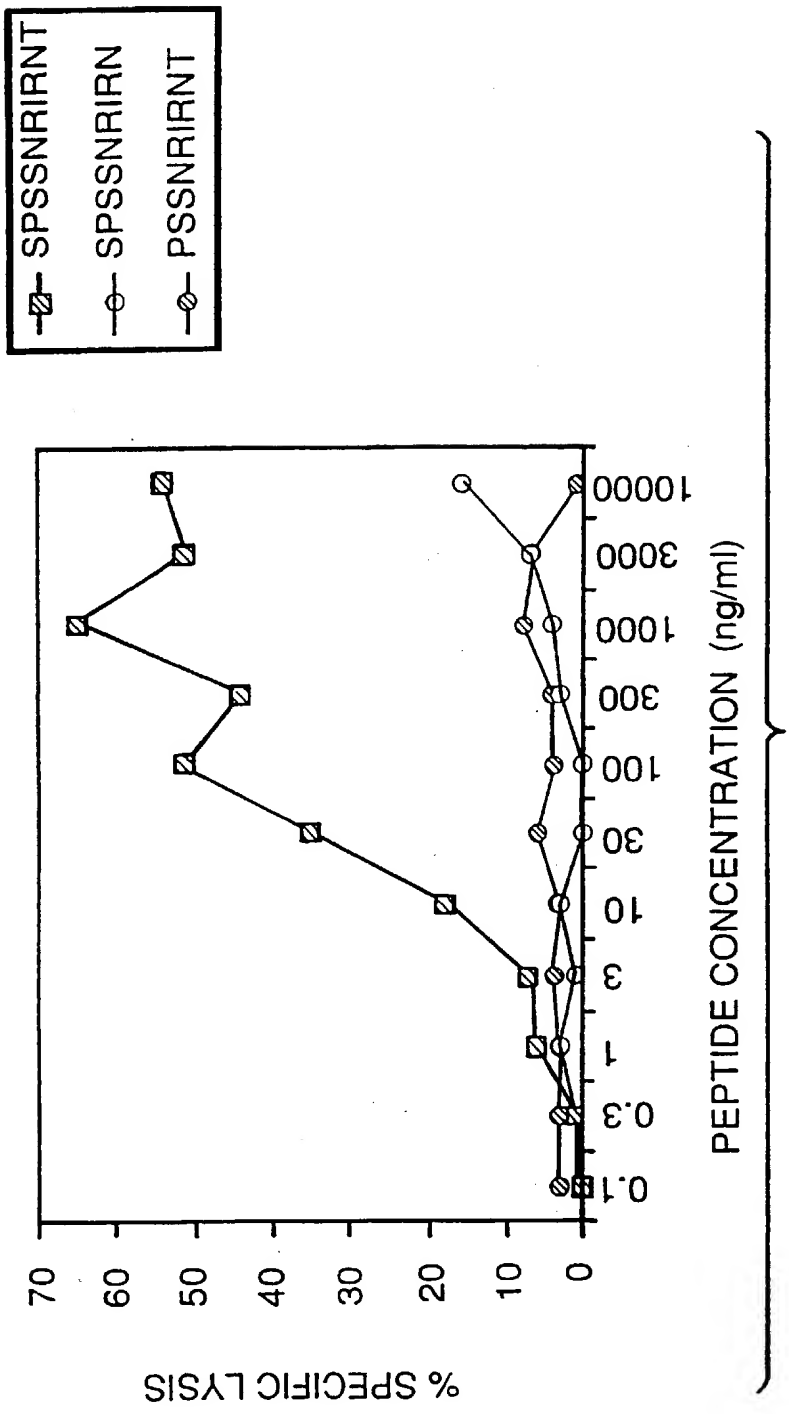

Fig. 5

BNSDOCID: <WO___9629409A2_I_>

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	**GB**	United Kingdom	**MW**	Malawi
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GA	Gabon	**MR**	Mauritania	**VN**	Viet Nam

BNSDOCID: <WO___9629409A3_I_>

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/US 96/04037

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/12 C07K14/705 C12N5/10 C12Q1/68 G01N33/574

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C12N C07K C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EMBL DATABASE, Accession number M91400 Sequence reference HSRTPGEU;21 July 1992 Compare with nucleotides 1079-1309 of SEQ. ID. NO. 1 XP002013013 .	23,24, 30-32
A	WO,A,94 05304 (LUDWIG INST CANCER RES) 17 March 1994 see the whole document	1-8
A	COLD SPRING HARBOR SYMPOSIA ON QUANTITATIVE BIOLOGY, vol. 59 The Molecular Genetics of Cancer, 1994, pages 617-622, XP000601971 T.BOON ET AL.: "Genes coding for tumor-specific rejection antigens"	1-40

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search
10 September 1996

Date of mailing of the international search report
27.09.96

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Authorized officer
Cupido, M

Form PCT/ISA/210 (second sheet) (July 1992)

BNSDOCID: <WO 9629409A3_I >

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 96/04037

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 19-22,39,40
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 19-22,39 and 40 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

BNSDOCID: <WO___9629409A3_I_>

INTERNATIONAL SEARCH REPORT

...formation on patent family members

Interr ...nal Application No
PCT/US 96/04037

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9405304	17-03-94	US-A-	5462871	31-10-95
		US-A-	5405940	11-04-95
		AU-B-	668772	16-05-96
		AU-A-	5096993	29-03-94
		AU-A-	6447594	24-10-94
		CA-A-	2143335	17-03-94
		CA-A-	2159098	13-10-94
		CN-A-	1093751	19-10-94
		EP-A-	0658113	21-06-95
		EP-A-	0690915	10-01-96
		FI-A-	950887	27-02-95
		FI-A-	954536	25-09-95
		JP-T-	8500837	30-01-96
		NO-A-	950660	24-02-95
		NO-A-	953699	20-11-95
		NZ-A-	263693	26-07-96
		WO-A-	9423031	13-10-94
		US-A-	5541104	30-07-96
		ZA-A-	9401644	12-10-94

BNSDOCID: <WO___9629409A3_I_>

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
L0461/6053WO		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US 99/ 22865	04/10/1999	05/10/1998
Applicant		
LUDWIG INSTITUTE FOR CANCER RESEARCH		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 6 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [X] contained in the international application in written form.

   [X] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [X] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [X] None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 99/22865

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 70-97 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet.

1. [X] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[X] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-104, all partially

MO-REN-22-5' renal tumour antigen precursor, nucleic acids encoding it, HLA-binding fragments of the protein, antibody against said protein or a complex of an HLA molecule with one of said fragments, use of said nucleic acid, protein or antibody in diagnosis, pharmaceutical composition comprising said protein, nucleic acid, HLA-complex or a cell expressing such a complex, expression vector encoding said protein, host cell comprising said expression vector, fragments of said nucleic acid and their use in detection of the nucleic acid, use of said peptide, nucleic acid, fragments or HLA-complex to selectively enrich a sample of a patients T-cells with T-cells reactive against said complex, fragment or protein.

2. Claims: 1-104, all partially

MO-REN-46 renal tumour antigen precursor, nucleic acids encoding it, HLA-binding fragments of the protein, antibody against said protein or a complex of an HLA molecule with one of said fragments, use of said nucleic acid, protein or antibody in diagnosis, pharmaceutical composition comprising said protein, nucleic acid, HLA-complex or a cell expressing such a complex, expression vector encoding said protein, host cell comprising said expression vector, fragments of said nucleic acid and their use in detection of the nucleic acid, use of said peptide, nucleic acid, fragments or HLA-complex to selectively enrich a sample of a patients T-cells with T-cells reactive against said complex, fragment or protein.

3. Claims: 1-104, all partially

MO-REN-54 renal tumour antigen precursor, nucleic acids encoding it, HLA-binding fragments of the protein, antibody against said protein or a complex of an HLA molecule with one of said fragments, use of said nucleic acid, protein or antibody in diagnosis, pharmaceutical composition comprising said protein, nucleic acid, HLA-complex or a cell expressing such a complex, expression vector encoding said protein, host cell comprising said expression vector, fragments of said nucleic acid and their use in detection of the nucleic acid, use of said peptide, nucleic acid, fragments or HLA-complex to selectively enrich a sample of a patients T-cells with T-cells reactive against said complex, fragment or protein.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

A meaningful search for the full scope of claims 1-36,42-47,61-67,70-95, and 98-104 could not be performed due to a lack of disclosure of the protein sequence of MO-REN-22 (nucleic acid; seq.ID.1) and lack of identification of the reading frame in which said sequence should be translated to obtain (part of) said protein sequence (Art.5 PCT). Consequently, the search has been limited to those parts of said claims which do not relate to said protein sequence or products/methods/compounds derived there from (e.g. peptide fragments, antibody, HLA complexes, etc.).

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.